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(54) Title: CYCLIC AMIDINO AGENTS USEFUL AS NITRIC OXIDE SYNTHASE INHIBITORS

(57) Abstract

The current invention discloses amidino derivatives of formula (I) useful as nitric oxide synthase inhibitors wherein R1 is selected from the group consisting of cycloalkyl, heterocyclyl and aryl, which may optionally be substituted; L is selected from the group consisting of lower alkynylene, and (CH2)m-D-(CH2)n-; D is selected from the group consisting of O, S, SO, SO2, SO2NR7, NR7SO2, NR8, POOR7, PON(R7)2, POOR7NR7, NR7POOR7, C(O), C(O)O; B is selected from the group consisting of (CH2)v, CH=CH; A is selected from the group consisting of O, NR7, (CH2)q, CH=CH; X is selected from the group consisting of NH, O, S, (CH2)p and CH=CH.
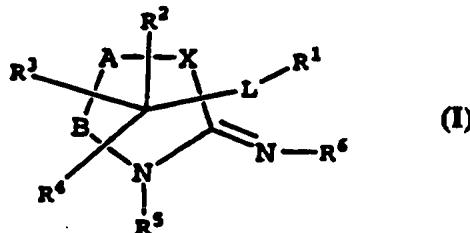
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CYCLIC AMIDINO AGENTS USEFUL AS
NITRIC OXIDE SYNTHASE INHIBITORS

5

CIP of US 08/425,831 filed April 20, 1995, contents of which are herein incorporated by reference.

10   ## Field of the Invention

The present invention relates to amidino derivative compounds, pharmaceutical compositions containing these novel compounds, and to their use in therapy, in particular

15   their use as nitric oxide synthase inhibitors.

Background of the Invention

It has been known since the early 1980's that the

20   vascular relaxation brought about by acetycholine is dependent on the presence of the endothelium and this activity was ascribed to a labile humoral factor termed endothelium-derived relaxing factor (EDRF). The activity of nitric oxide (NO) as a vasodilator has been known for

25   well over 100 years and NO is the active component of amylnitrite, glyceryltrinitrite and other nitrovasodilators. The recent identification of EDRF as NO has coincided with the discovery of a biochemical pathway by which NO is synthesized from the amino acid

30   L-arginine by the enzyme NO synthase.

NO is the endogenous stimulator of the soluble guanylate cyclase and is involved in a number of biological actions in addition to endothelium-dependent relaxation

35   including cytotoxicity of phagocytic cells and cell-to-cell communication in the central nervous system (see Moncada et al, Biochemical Pharmacology, 38, 1709-1715 (1989) and Moncada et al, Pharmacological Reviews, 43, 109-142 (1991).

It is now thought that excess NO production may be
involved in a number of conditions, particularly
conditions which involve systemic hypotension such as
toxic shock and therapy with certain cytokines.

The synthesis of NO from L-arginine can be
inhibited by the L-arginine analogue, L-N-monomethyl-
arginine (L-NMMA) and the therapeutic use of L-NMMA for
the treatment of toxic shock and other types of systemic
hypotension has been proposed (WO 91/04024 and GB-A-
2240041). The therapeutic use of certain other NO
synthase inhibitors apart from L-NMMA for the same
purpose has also been proposed in WO 91/04024 and in EP-
A-0446699.

It has recently become apparent that there are at
least three types of NO synthase as follows:
    (i)   a constitutive, Ca^{++}/calmodulin dependent
enzyme, located in the endothelium, that releases NO in
response to receptor or physical stimulation.
    (ii)   a constitutive, Ca^{++}/calmodulin dependent
enzyme, located in the brain, that releases NO in
response to receptor or physical stimulation.
    (iii) a Ca^{++} independent enzyme which is induced
after activation of vascular smooth muscle, macrophages,
endothelial cells, and a number of other cells by
endotoxin and cytokines. Once expressed this inducible
NO synthase synthesizes NO for long periods.

The NO released by the constitutive enzymes acts as
a transduction mechanism underlying several physiological
responses. The NO produced by the inducible enzyme is a
cytotoxic molecule for tumor cells and invading
microorganisms. It also appears that the adverse effects
of excess NO production, in particular pathological
vasodilation and tissue damage, may result largely from
the effects of NO synthesized by the inducible NO
synthase.

There is also a growing body of evidence that NO may be involved in the degeneration of cartilage which takes place in certain conditions such as arthritis and it is also known that NO synthesis is increased in rheumatoid arthritis. Accordingly, further conditions in which there is an advantage in inhibiting NO production from L-arginine include autoimmune and/or inflammatory conditions affecting the joints, for example arthritis, inflammatory bowel disease, cardiovascular ischemia, diabetes, hyperalgesia (allodynia), cerebral ischemia (both focal ischemia, thrombotic stroke and global ischemia, secondary to cardiac arrest), and other CNS disorders mediated by NO.

Futher conditions in which there is an advantage in inhibiting NO production from L-arginine include systemic hypotension associated with septic and/or toxic shock induced by a wide variety of agents; therapy with cytokines such as TNF, IL-1 and IL-2; and as an adjuvant to short term immunosuppression in transplant therapy. Further conditions in which there is an advantage in inhibiting NO production from L-arginine include autoimmune diseases and/or inflammatory conditions such as those affecting the joints, for example arthritis or ARDS or inflammatory bowel disease, or asthma, cardiovascular ischemia, congestive heart failure, myocarditis, artherosclerosis, migraine, reflux esophagitis, diarrhea, irritable bowel syndrome, cystic fibrosis, emphysema, diabetes, hyperalgesia (allodynia) cerebral ischemia (both focal ischemia, thrombotic stroke and global ischemia, secondary to cardiac arrest) and other CNS disorders mediated by NO, including opiate tolerance in patients needing protracted opiate analgesics, benzodiazepine tolerance in patients taking benzodiazepines, and other addictive behaviors for example nicotine and eating disorder.

Some of the NO synthase inhibitors proposed for therapeutic use so far, and in particular L-NMMA, are non-selective in that they inhibit both the constitutive

5   and the inducible NO synthase. Use of such a non-selective NO synthase inhibitor requires that great care be taken in order to avoid the potentially serious consequences of over-inhibition of the constitutive NO-synthase including hypertension and possible thrombosis

10   and tissue damage. In particular, in the case of the therapeutic use of L-NMMA for the treatment of toxic shock it has been recommended that the patient must be subject to continuous blood pressure monitoring throughout the treatment. Thus, while non-selective NO

15   synthase inhibitors have therapeutic utility provided that appropriate precautions are taken, NO synthase inhibitors which are selective in the sense that they inhibit the inducible NO synthase to a considerably greater extent than the constitutive isoforms of NO

20   synthase would be of even greater therapeutic benefit and easier to use.

WO94/12165, WO94/14780, WO93/13055, EP0446699A1 and U.S. Patent No. 5,132,453 disclose compounds that inhibit

25   nitric oxide synthesis and preferentially inhibit the inducible isoform of nitric oxide synthase. The disclosures of which are hereby incorporated by reference in their entirety as if written herein.

30   Summary of the Invention

In accordance with the present invention novel amidino derivative are provided. These novel inhibitor compounds can be represented by the following chemical

35   formula (I):

$$
\begin{array}{c}
R^2 \\
A\!-\!|\!-\!X \qquad R^1 \\
R^3 \diagdown \quad | \qquad \diagup L \\
B \diagdown \qquad \diagup \\
\qquad N\!-\!R^6 \\
R^4 \qquad N \\
| \\
R^5
\end{array}
$$
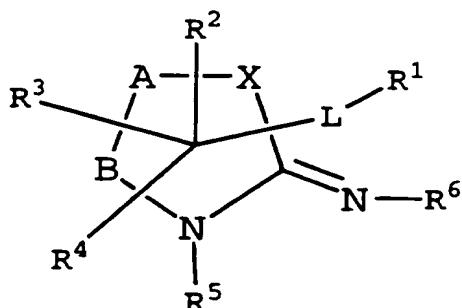
(I)

R^1 is selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl which may optionally be substituted by one or more of the following: lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, $S(O)R^9$, $S(O)_2R^9$, halogen, nitro, amino, alkylamino, dialkylamino, aminoalkyl, dialkylaminoalkyl, arylamino, aminoaryl, alkylaminoaryl, acylamino, carboxyl, carboalkoxy, carboaryloxy, carboarylalkyloxy, cyano, aminocarbonylalkoxy, aminocarbonylamino, aminocarbonylaminoalkyl, haloalkyl, $SO_2NR^7R^9$, wherein all said substitutions may be optionally substituted with one or more of the following: halogen, lower alkyl, amino, alkylamino, dialkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy;

L is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, and $-(CH_2)_m-D-(CH_2)_n-$;

D is selected from the group consisting of O, S, SO, SO_2, SO_2NR^7, NR^7SO_2, NR^8, $POOR^7$, $PON(R^7)_2$, $POOR^7NR^7$, NR^7POOR^7, $C(O)$, $C(O)O$;

R^7 is hydrogen, lower alkyl, or aryl;

R^8 is hydrogen, lower alkyl, COR^9, or CO_2R^9;

R^9 is lower alkyl, or aryl;

m = 0 to about 7;

n = 0 to about 5;

wherein L may optionally be substituted by one or more of the following lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, $S(O)R^9$, $S(O)_2R^9$, halogen, nitro, amino, alkylamino, dialkylamino, aminoalkyl, dialkylaminoalkyl, arylamino, aminoaryl, alkylaminoaryl, acylamino, carboxyl, carboalkoxy, carboaryloxy, carboarylalkyloxy, cyano, aminocarbonylalkoxy, aminocarbonylamino, aminocarbonylaminoalkyl, haloalkyl, $SO_2NR^7R^9$, cycloalkyl, heterocyclyl, aryl, heteroaryl, lactonyl, lactamyl, amidino, isourea, isothiourea, guanidino, substituted guanidino, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, amino, alkylamino, dialkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy, nitro, amidino, guanidino, substituted guanidino and

X is selected from the group consisting of NH, O, S, $(CH_2)_p$, and CH=CH;

p = 0 to about 4;

A is selected from the group consisting of $(CH_2)_q$, CH=CH;

q = 1 to about 2;

B is selected from the group consisting of $(CH_2)_v$, CH=CH;

v = 1 to about 2;

R^2, R^3, and R^4 are independently selected from
hydrogen, lower alkyl, lower alkenyl, lower alkynyl,
hydroxy, lower alkoxy, thiol, lower thioalkoxy, $S(O)R^9$,
$S(O)_2R^9$, halogen, nitro, amino, alkylamino, dialkylamino,

5   aminoalkyl, dialkylaminoalkyl, arylamino, aminoaryl,
alkylaminoaryl, acylamino, carboxyl, carboalkoxy,
carboaryloxy, carboarylalkyloxy, cyano,
aminocarbonylalkoxy, aminocarbonylamino,
aminocarbonylaminoalkyl, haloalkyl, $SO_2NR^7R^9$, wherein all

10   said substitutions may be optionally substituted with one
or more of the following: halogen, lower alkyl, amino,
alkylamino, dialkylamino, aminoalkyl, aminoacyl,
carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy,
hydroxy, lower alkoxy, and

15

and R^2, R^3, may optionally be taken together to form an
exocyclic double bond, alicyclic hydrocarbon,
heterocyclyl or aromatic hydrocarbon and said optionally
formed unit may be optionally substituted with one or

20   more of the following:

lower alkyl, lower alkenyl, lower alkynyl which may be
optionally substituted with carboxyl, carboalkoxy,
carboaryloxy, carboxyalkylaryloxy and lower alkoxy; and

25

R^5, R^6 are independently selected from the group
consisting of hydrogen, hydroxy, and alkyloxy.

In another broad aspect, the present invention is

30   directed to inhibiting nitric oxide synthesis in a
subject in need of such inhibition or treatment by
administering a compound of Formula (I) which
preferentially inhibits the inducible isoform of nitric
oxide synthase over the constitutive isoform of nitric

35   oxide synthase, in a nitric oxide synthesis inhibiting
amount to such subject.

The invention further relates to a pharmaceutical composition comprising a compound from Formula (I).

Compounds and compositions defined above have usefulness as inhibitors of nitric oxide synthase. These compounds also preferentially inhibit the inducible form.

Conditions in which there is an advantage in inhibiting NO production from L-arginine in disorders mediated by nitric oxide including amongst others, systemic hypotension associated with septic and/or toxic shock induced by a wide variety of agents; therapy with cytokines such as TNF, IL-1 and IL-2; and as an adjuvant to short term immunosuppression in transplant therapy. Further conditions in which there is an advantage in inhibiting NO production from L-arginine include autoimmune diseases and/or inflammatory conditions such as those affecting the joints, for example arthritis or inflammatory bowel disease, cardiovascular ischemia, diabetes, congestive heart failure, myocarditis, artherosclerosis, migraine, reflux esophagitis, diarrhea, irritable bowel syndrome, cystic fibrosis, emphysema, hyperalgesia (allodynia) cerebral ischemia (both focal ischemia, thrombotic stroke and global ischemia, secondary to cardiac arrest) and other CNS disorder mediated by NO, including opiate tolerance in patients needing protracted opiate analogesics, benzodiazepine tolerance in patients taking benzodiazepines, and other addictive behaviors for example nicotine and eating disorder.

The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the

compound in question. Thus, preferred salts include
those formed from hydrochloric, hydrobromic, sulfuric,
citric, tartaric, phosphoric, lactic, acetic, succinic,
fumaric, maleic, methanesulfonic, ethanesulfonic,p-

5   toluenesulfonic, benzenesulfonic and the like. (See, for
example, S. M. Berge et al., Pharmaceutical Salts, *J.
Pharm. Sci.*, 1977, *66*, 1-19.) Salts of the compounds of
formula (I) can be made by reacting the appropriate
compound in the form of the free base with the

10   appropriate acid.

     While it may be possible for the compounds of
formula (I) to be administered as the raw chemical, it is
preferable to present them as a pharmaceutical

15   formulation. According to a further aspect, the present
invention provides a pharmaceutical formulation
comprising a compound of formula (I) or a
pharmaceutically acceptable salt or solvate thereof,
together with one or more pharmaceutically acceptable

20   carriers thereof and optionally one or more other
therapeutic ingredients. The carrier(s) must be
"acceptable" in the sense of being compatible with the
other ingredients of the formulation and not deleterious
to the recipient thereof.

25

     The formulations include those suitable for oral,
parenteral (including subcutaneous, intradermal,
intramuscular, intravenous and intraarticular), rectal
and topical (including dermal, buccal, sublingual and

30   intraocular) administration although the most suitable
route may depend upon for example the condition and
disorder of the recipient. The formulations may
conveniently be presented in unit dosage form and may be
prepared by any of the methods well known in the art of

35   pharmacy. All methods include the step of bringing into
association a compound of formula (I) or a
pharmaceutically acceptable salt or solvate thereof
("active ingredient") with the carrier which constitutes

one or more accessory ingredients. In general, the
formulations are prepared by uniformly and intimately
bringing into association the active ingredient with
liquid carriers or finely divided solid carriers or both
5   and then, if necessary, shaping the product into the
desired formulation.

Formulations of the present invention suitable for
oral administration may be presented as discrete units
10 such as capsules, cachets or tablets each containing a
predetermined amount of the active ingredient; as a
powder or granules; as a solution or a suspension in an
aqueous liquid or a non-aqueous liquid; or as an oil-in-
water liquid emulsion or a water-in-oil liquid emulsion.
15 The active ingredient may also be presented as a bolus,
electuary or paste.

A tablet may be made by compression or moulding,
optionally with one or more accessory ingredients.
20 Compressed tablets may be prepared by compressing in a
suitable machine the active ingredient in a free-flowing
form such as a powder or granules, optionally mixed with
a binder, lubricant, inert diluent, lubricating, surface
active or dispersing agent. Moulded tablets may be made
25 by moulding in a suitable machine a mixture of the
powdered compound moistened with an inert liquid diluent.
The tablets may optionally be coated or scored and may be
formulated so as to provide slow or controlled release of
the active ingredient therein.
30

Formulations for parenteral administration include
aqueous and non-aqueous sterile injection solutions which
may contain antioxidants, buffers, bacteriostats and
solutes which render the formulation isotonic with the
35 blood of the intended recipient; and aqueous and non-
aqueous sterile suspensions which may include suspending
agents and thickening agents. The formulations may be
presented in unit-dose or multi-dose containers, for

example sealed ampoules and vials, and may be stored in a
freeze-dried (lyophilized) condition requiring only the
addition of the sterile liquid carrier, for example,
saline, water-for-injection, immediately prior to use.
5   Extemporaneous injection solutions and suspensions may be
prepared from sterile powders, granules and tablets of
the kind previously described.

Formulations for rectal administration may be
10   presented as a suppository with the usual carriers such
as cocoa butter or polyethylene glycol.

Formulations for topical administration in the
mouth, for example buccally or sublingually, include
15   lozenges comprising the active ingredient in a flavored
basis such as sucrose and acacia or tragacanth, and
pastilles comprising the active ingredient in a basis
such as gelatin and glycerin or sucrose and acacia.

20   Formulations for administration by inhalation can
be prepared for use as an aerolized medicaments such as
in a manner recited in US 5,458,135 and US 5,447,150.

Preferred unit dosage formulations are those
25   containing an effective dose, as hereinbelow recited, or
an appropriate fraction thereof, of the active
ingredient.

It should be understood that in addition to the
30   ingredients particularly mentioned above, the
formulations of this invention may include other agents
conventional in the art having regard to the type of
formulation in question, for example those suitable for
oral administration may include flavoring agents.
35

The compounds of the invention may be administered
orally or via injection at a dose of from 0.001 to 2500
mg/kg per day. The dose range for adult humans is

generally from 0.005 mg to 10 g/day. Tablets or other
forms of presentation provided in discrete units may
conveniently contain an amount of compound of the
invention which is effective at such dosage or as a
5   multiple of the same, for instance, units containing 5 mg
to 500 mg, usually around 10 mg to 200 mg.

The compounds of formula (I) are preferably
administered orally or by injection (intravenous or
10 subcutaneous). The precise amount of compound
administered to a patient will be the responsibility of
the attendant physician. However, the dose employed will
depend on a number of factors, including the age and sex
of the patient, the precise disorder being treated, and
15 its severity. Also, the route of administration may vary
depending on the condition and its severity.

As utilized herein, the term "lower alkyl", alone
or in combination, means an acyclic alkyl radical
20 containing from 1 to about 10, preferably from 1 to about
8 carbon atoms and more preferably 1 to about 6 carbon
atoms. Examples of such radicals include methyl, ethyl,
n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-
butyl, pentyl, iso-amyl, hexyl, octyl and the like.
25

The term "lower alkenyl" refers to an unsaturated
acyclic hydrocarbon radical in so much as it contains at
least one double bond. Such radicals containing from
about 2 to about 10 carbon atoms, preferably from about 2
30 to about 8 carbon atoms and more preferably 2 to about 6
carbon atoms. Examples of suitable alkenyl radicals
include propylenyl, buten-1-yl, isobutenyl, pentenylen-1-
yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl,
hepten-1-yl, and octen-1-yl, and the like.
35

The term "lower alkynyl" refers to an unsaturated
acyclic hydrocarbon radical in so much as it contains one
or more triple bonds, such radicals containing about 2 to

about 10 carbon atoms, preferably having from about 2 to about 8 carbon atoms and more preferably having 2 to about 6 carbon atoms. Examples of suitable alkynyl radicals include ethynyl, propynyl, butyn-1-yl, butyn-2-

5 yl, pentyn-1-yl, pentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

The term "alicyclic hydrocarbon" or "cycloalkyl"
10 means a aliphatic radical in a ring with 3 to about 10 carbon atoms, and preferably from 3 to about 6 carbon atoms. Examples of suitable alicyclic radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl and the like.

15   The term "aromatic hydrocarbon radical" means 4 to about 16 carbon atoms,preferably 6 to about 12 carbon atoms, more preferably 6 to about 10 carbon atoms. Examples of suitable aromatic hydrocarbon radicals include phenyl,naphthyl, and the like.

20

The term "aryl" as used herein means 5- and 6-membered single-aromatic radicals which may include from zero to four heteroatoms. Representative aryls include phenyl, thienyl, furanyl, pyridinyl, (is)oxazoyl and the
25 like.

The term DCM means dichloromethane.

The term DEAD means diethyl azodicarboxylate.

30   The term DIBAL-H means diisobutylaluminum hydride.

The term DMAP means dimethylaminopyridine.

The term DMSO means dimethylsulfoxide.
35

The term EDC means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

The term "heterocyclyl radical" means a saturated or unsaturated cyclic hydrocarbon radical including aromatic systems with 4 to about 10 carbon atoms, preferably about 5 to about 6; wherein 1 to about 4

5   carbon atoms are replaced by nitrogen, oxygen, sulfur, or carbonyl. The "heterocyclic radical" may be fused to an aromatic hydrocarbon radical. Suitable examples include pyrrolyl, pyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl,

10   indolyl, thienyl, furanyl, tetrazolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolindinyl, 1,3-dioxolanyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolinyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, 2H-pyranyl, 4H-pyranyl,

15   piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, quinolinyl, and the like.

20   The term HOBT means N-hydroxybenzotriazole.

         The term "lower alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above and most preferably containing 1 to about 4

25   carbon atoms. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

         The term "lower thioalkoxy", alone or in

30   combination, means an alkyl thioether radical wherein the term alkyl is as defined above and most preferably containing 1 to about 4 carbon atoms. Examples of suitable alkyl thioether radicals include thiomethoxy, thioethoxy, thio-n-propoxy, thio-i-propoxy, thio-n-

35   butoxy, thio-iso-butoxy, thio-sec-butoxy, thio-tert-butoxy and the like.

The term alkoxycarbonyl as used herein means an alkoxy group, as defined above, having a carbonyl (C=O) group attached.

5   The term "halogen" means fluorine, chlorine, bromine or iodine.

The term mcpba means m-chloroperbenzoic acid.

10   The term NMM means N-methylmorpholine.

The term NMMO means 4-methylmorpholine N-oxide.

The term "prodrug" refers to a compound that is
15   made more active *in vivo*.

The term sulfinyl means SO.

The term sulfonyl means SO_2.
20

The term TEA means triethylamine.

The term $TMSN_3$ means azidotrimethylsilane.

25   As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated
30   by reference as if written herein.

Compounds of the present invention can exist in geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and
35   trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof, as falling within the scope of the invention.

Disclosed are nineteen general synthetic processes useful in the preparation of the compounds of the present invention.

Scheme 1:
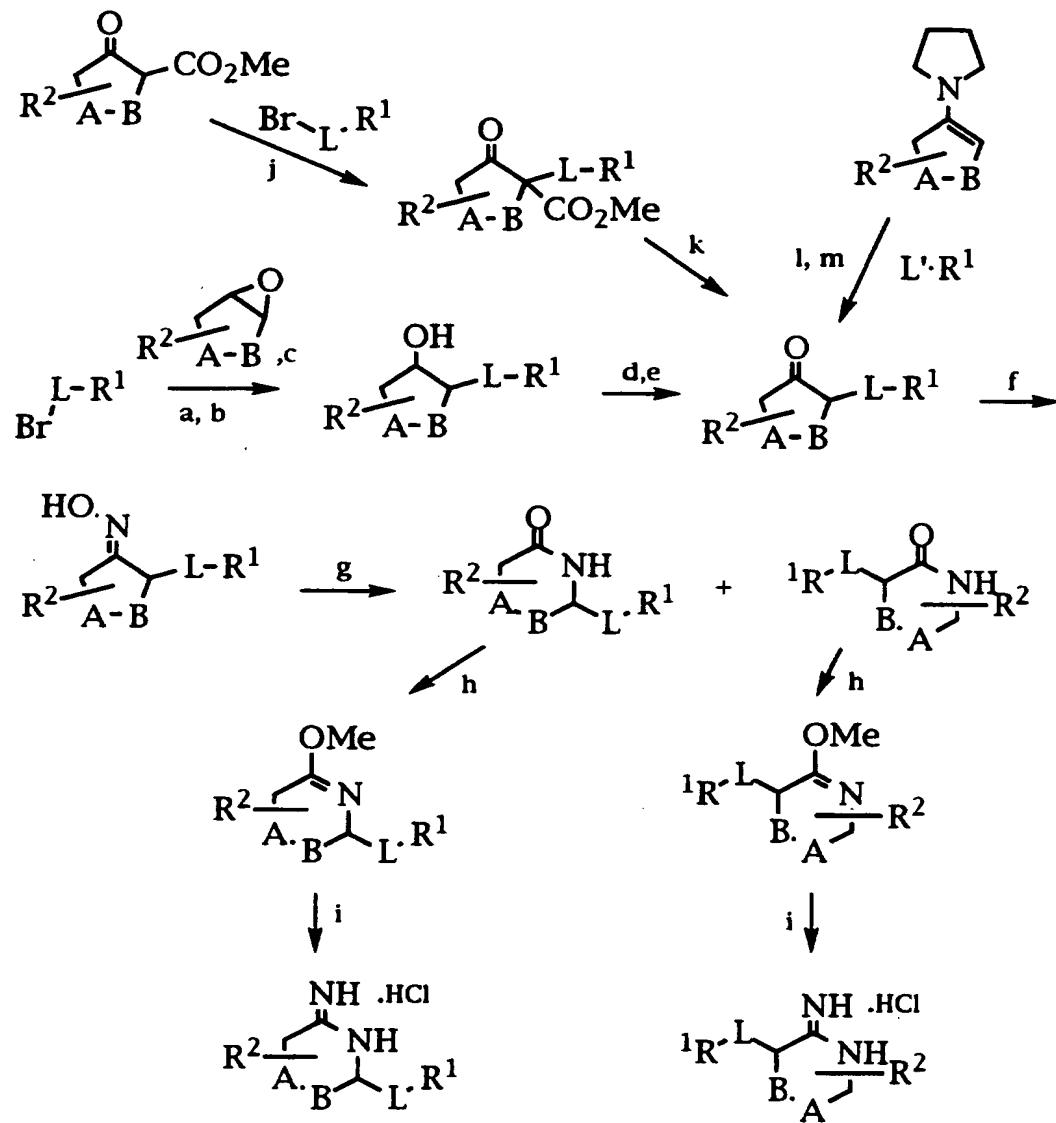
a) Mg, THF;   b) CuI, -30 °C;   c)   -30 °C to 0 °C or r.t.;   d) DMSO, oxalyl chloride, CH_2Cl_2, -70 °C;   e) Et_3N, -70 °C to 0 °C;   f) NH_2OH, NaOAc, EtOH;   g) $PhSO_2Cl$, NaOH, H_2O, acetone [followed by resolution and or H_2, Pd/C reduction where R^1 = phenyl];   h) Me_3O^+ BF_4^-;   i) NH_4Cl;   j) K_2CO_3 or NaH, DMF;   k) NaCN DMSO, H_2O, heat;   l) DMF, L- R^1 (where L'-R^1 is $CH_2=CHCO-R^1$);   m)   1N LiOH, MeOH.

Scheme 2:
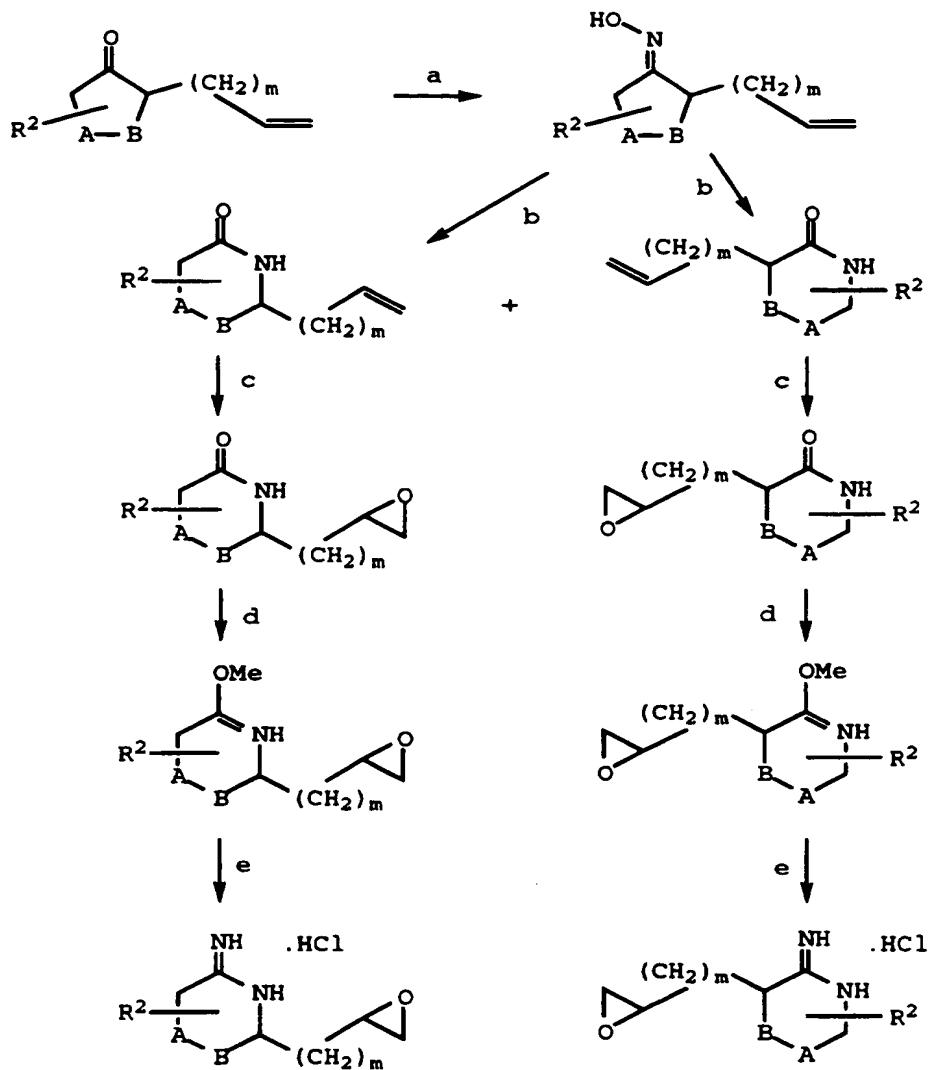
a) NH$_2$OH, NaOAc, EtOH;   b) PhSO$_2$Cl, NaOH, H$_2$O, acetone;   c)   m-chloroperbenzoic acid, CH$_2$Cl$_2$;   d) Me$_3$O$^+$ BF$_4$$^-$, CH$_2Cl_2$;   e) NH$_4$Cl, MeOH.

Scheme 3:

a) NaH, DMF;   b) Ph₃P, diethylazodicarboxylate
(DEAD), THF;   c) Me₃O⁺ BF₄⁻, CH₂Cl₂;   d) NH₄Cl, MeOH;
e) acetic anhydride, pyridine.

Scheme 4:

a) Pd(OAc)$_2$, tri-o-tolylphosphine, Et$_3$N, MeCN, where R^1 = substituted or unsubstituted aromatic or heteroaromatic; b) Me$_3$O$^+$ BF$_4^-$, CH$_2$Cl$_2$; c) NH$_4$Cl, MeOH; d) H$_2$, Pd/C.

Scheme 5:

a) Cl_3CN, NaH, xylene, D;   b) Ru catalyst;   c) Bu_3SNH;
d) Me_3O^+ BF_4^-, CH_2Cl_2;   e) NH_4Cl, MeOH.

Scheme 6:

a) Base;   b) H_2 / RaNi, 55 °C;   c) Me_3O^+ BF_4^-, CH_2Cl_2;
d) NH_4Cl, MeOH

Scheme 7:

a) R^2COR^3;   b) Base, $R^4CH_2CO_2Me$;   c) H_2/RaNi, 55°C;
d) Me_3O^+ BF_4^-;   e) NH_4Cl

Scheme 8:

a) HCl;   b) $Zn/BrCH_2Heterocycle$;   c) Et_3SiH;
d) Me_3O^+ BF_4^-; e) NH_4Cl, MeOH

Scheme 9:

a) HCl;   b) Zn/BrCH$_2$Heterocycle-CO$_2$Et;   c)
NaOH, MeOH;   d) t-butyldimethylsilyl
chloride (TBDMSCl);   e)   Me$_3$O$^+$ BF$_4^-$,CH$_2$Cl$_2$;
f) NH$_4$Cl, MeOH;   f) HCl.

Scheme 10:

a)   H$_2$, Rh/C, HOAc or H$_2$, PtO$_2$/C, HOAc

Scheme 11:

Y = Aryl, CF$_3$, alkoxycarbonyl
Z = 5-membered ring heterocycle (containing 1-4 N, and/or
O, and/or S),
phenyl or pyridyl substituted with 1-3 groups defined
such as: CO$_2$H,
alkoxycarbonyl, SO$_2$NH$_2$, SO$_3$H, alkylsulfonamides, and
nitro.

a) Et$_3$N, toluene; b) Me$_3$O$^+$BF$_4^-$, CH$_2$Cl$_2$; c) NH$_4$Cl,
CH$_3$OH; d) DDQ, Benzene.

Scheme 12:

Y = Aryl, CF$_3$, alkoxycarbonyl

a) Et$_3$N, diethyl ether (or toluene);   b) Me$_3$O$^+$BF$_4$$^-$, CH$_2Cl_2$;
c) NH$_4$Cl, CH$_3$OH;   d) MnO$_2$, Benzene/dioxane.
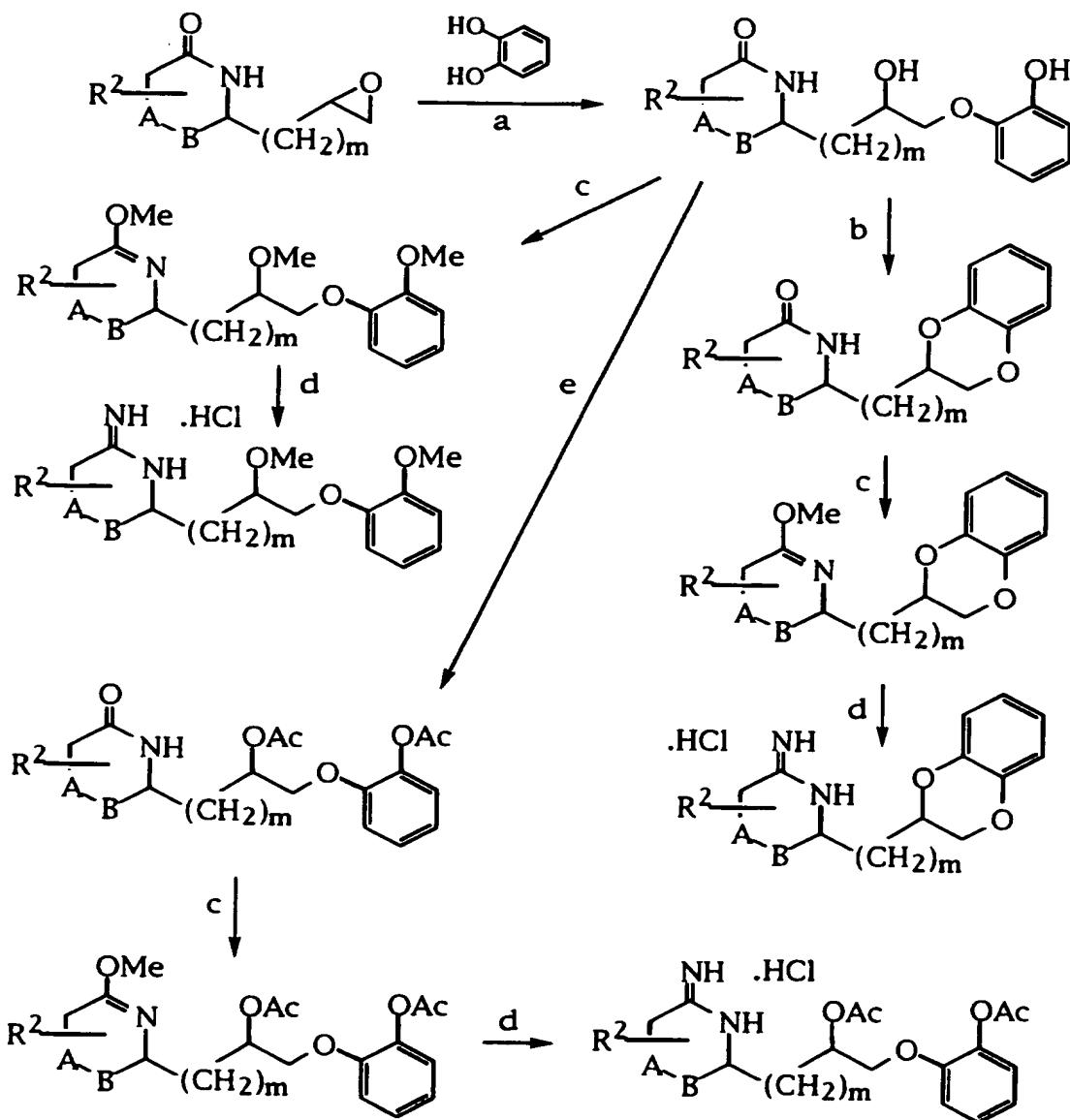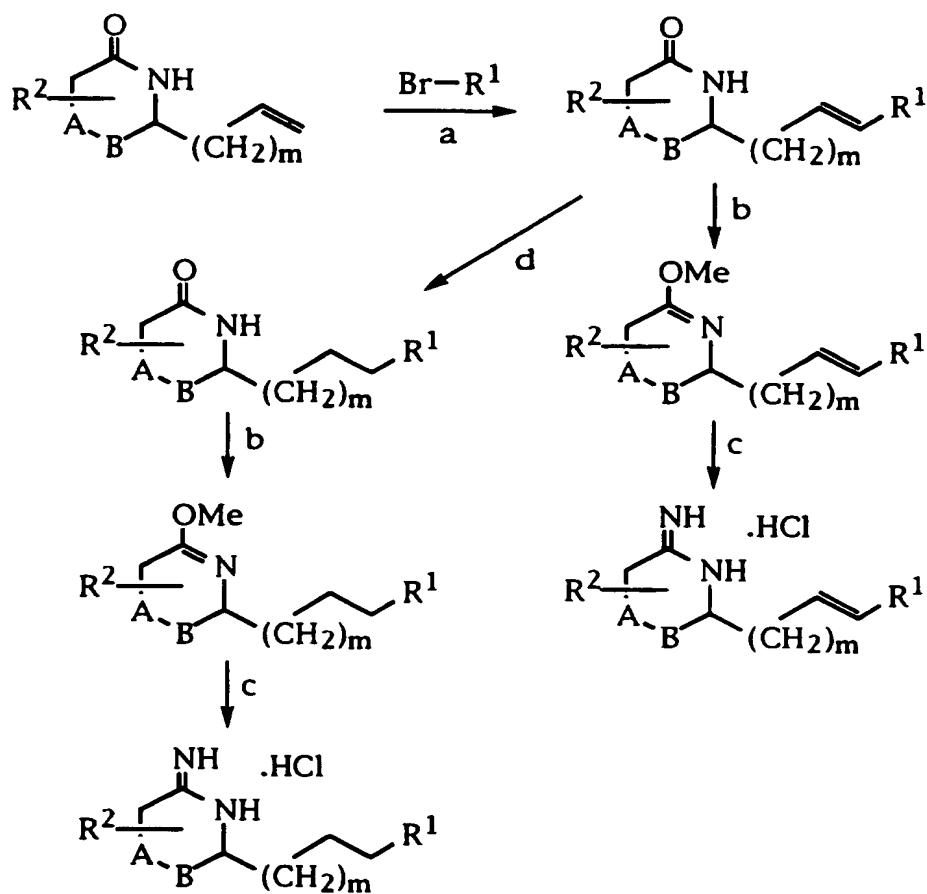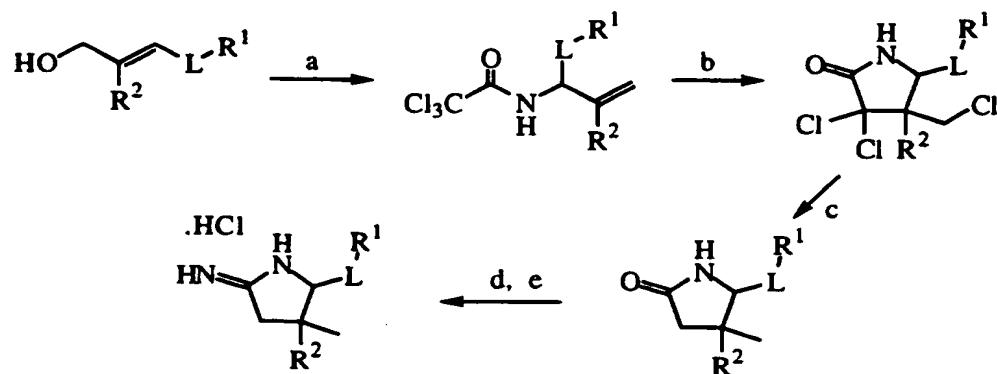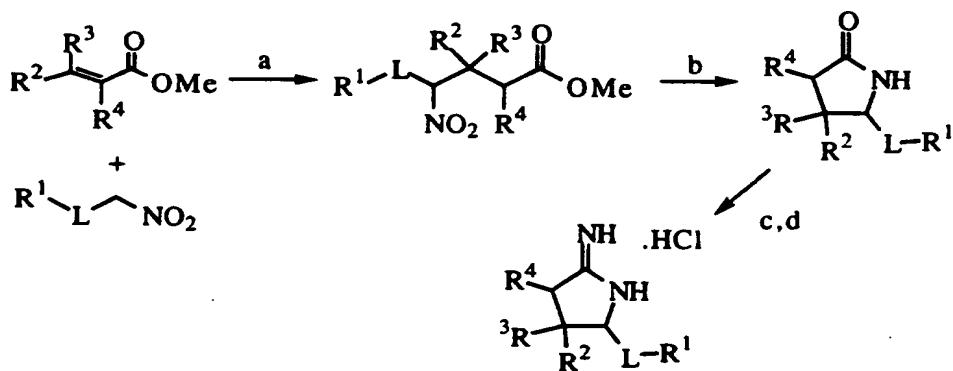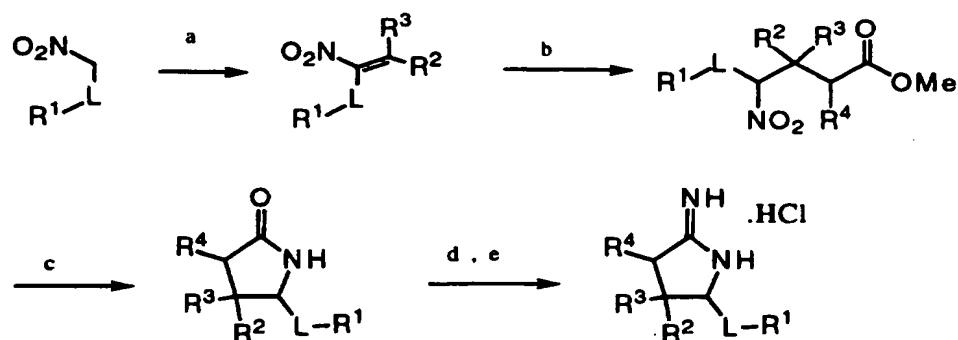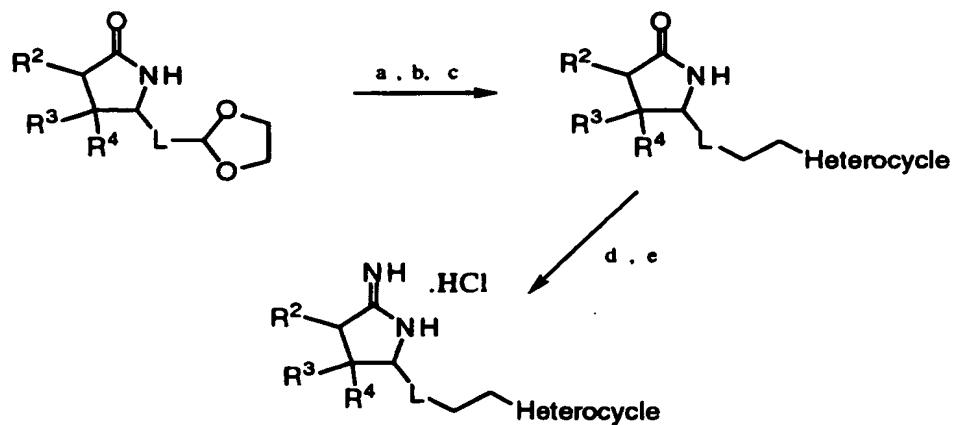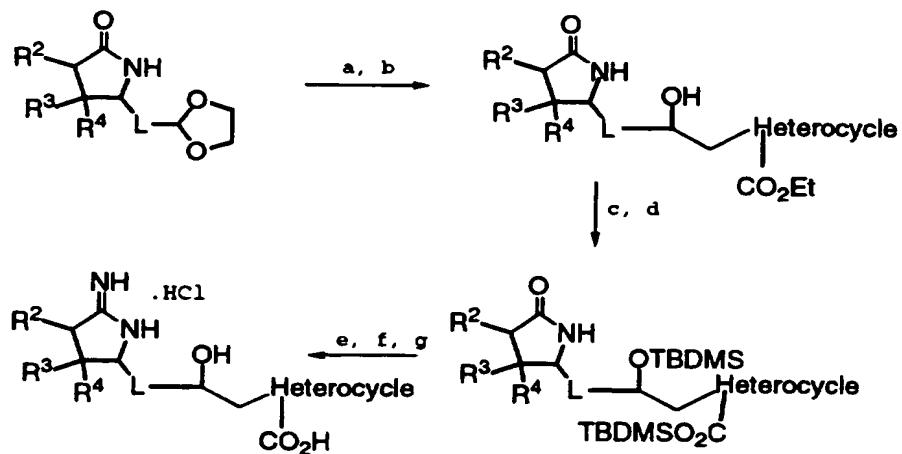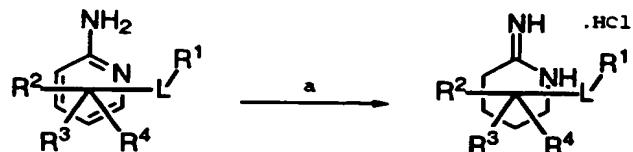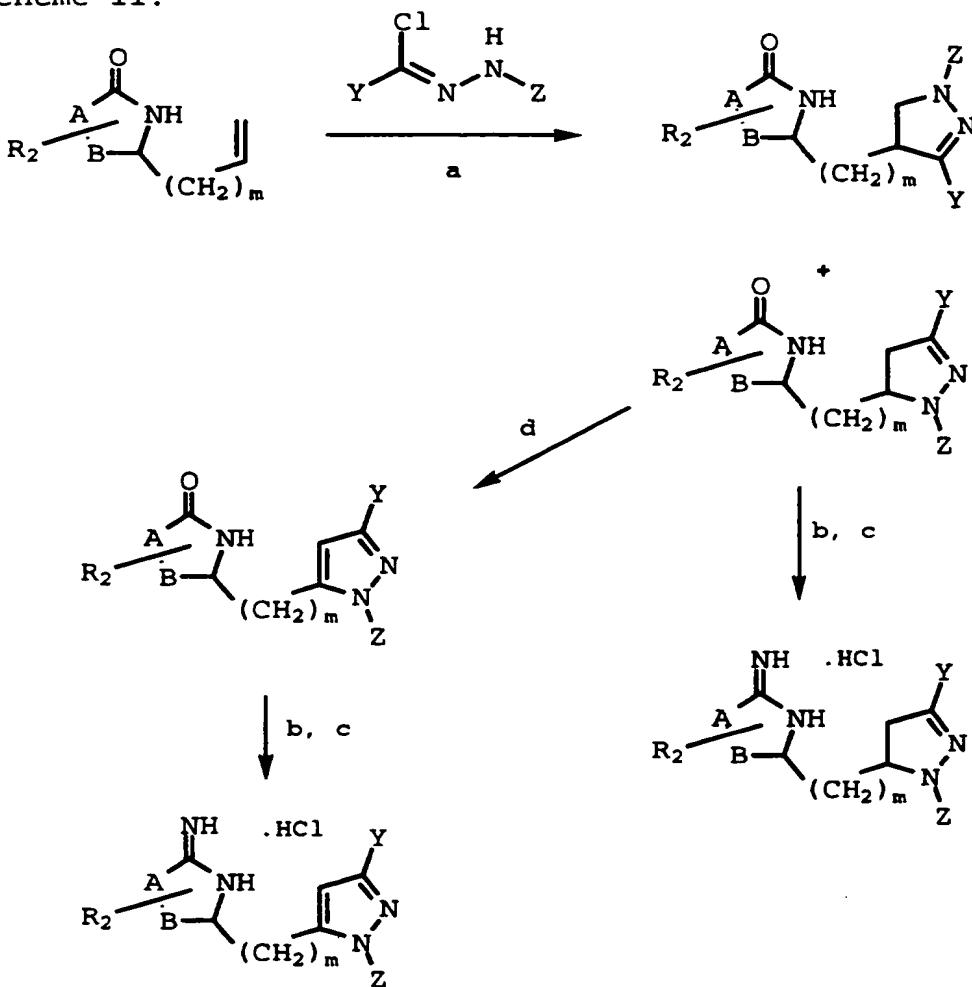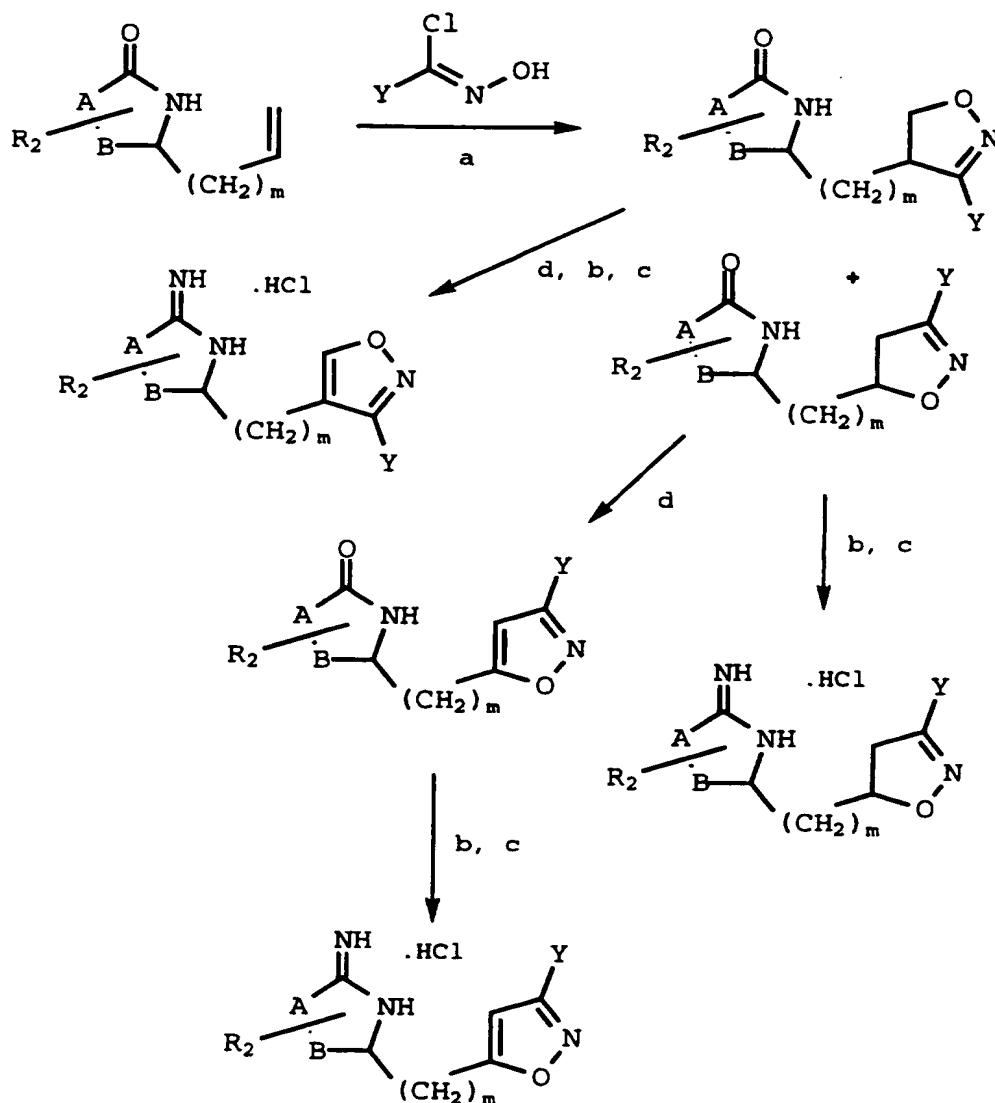
Scheme 13:
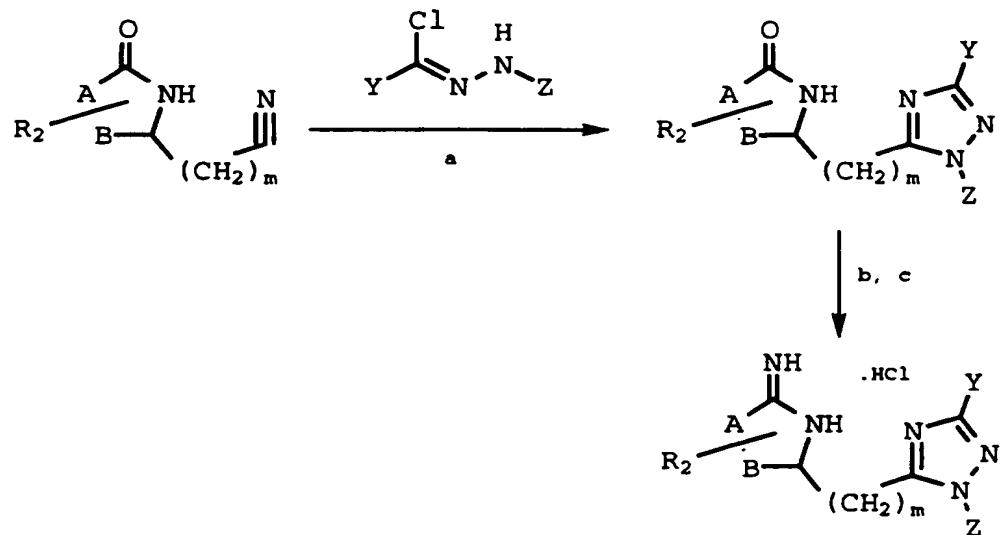
Y = Aryl, CF$_3$, alkoxycarbonyl

Z = 5-membered ring heterocycle (containing 1-4 N,
and/or O, and/or S),

phenyl or pyridyl substituted with 1-3 groups defined
such as: CO$_2$H, alkoxycarbonyl, SO$_2$NH$_2$, SO$_3$H,
alkylsulfonamides, nitro.

a) Et$_3$N, toluene;   b)   Me$_3$O$^+$BF$_4^-$, CH$_2$Cl$_2$;   c)   NH$_4$Cl, CH$_3$OH.

Scheme 14:
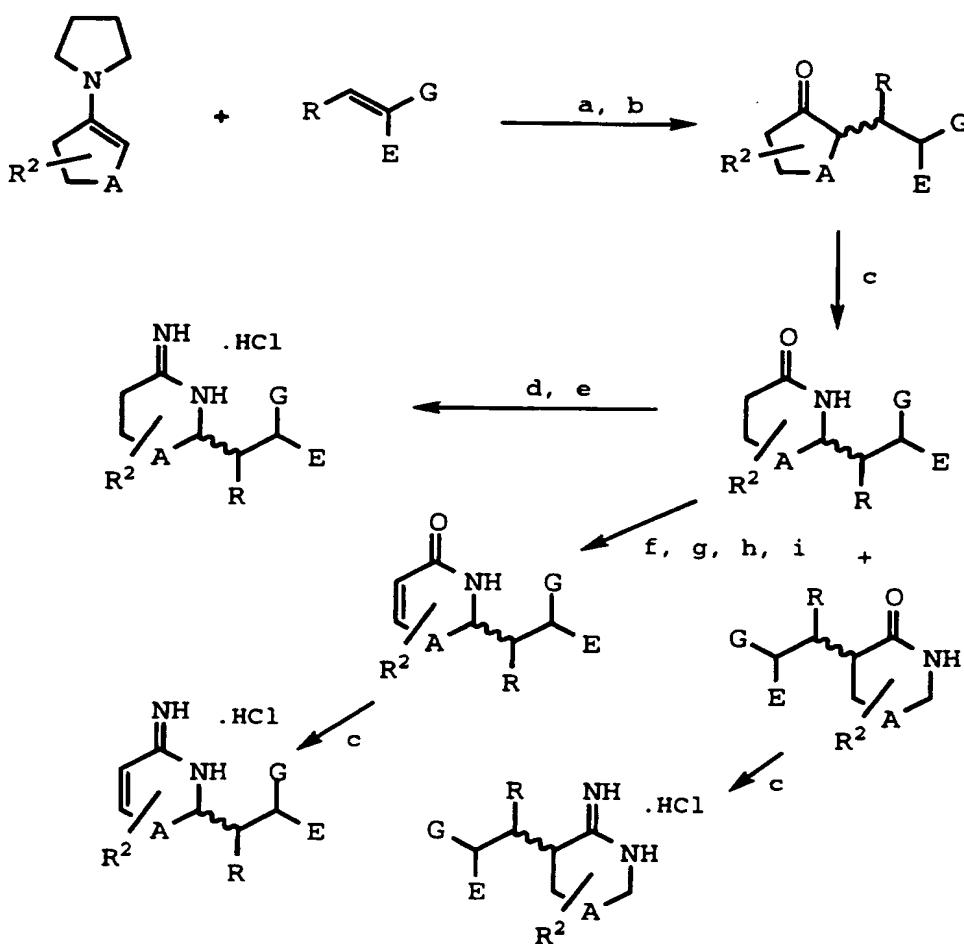
R = Hydrogen, amino, alkyl, alkenyl, alkynyl, carboxyl, ester, phenyl, halogen, alkoxy, heterocyclic, carbocyclic radicals wherein all said radicals may optionally substituted;

E = Cyano, carboxyl, ester, nitro, heterocylic;

G = Hydrogen, alkyl, haloalkyl, carboxyalkyl, carboxyl, ester;

R and G can form a carbocyclic ring containing 4-7 carbon atoms.

a) DMF, reflux, 24 h; add H_2O, reflux, 1h; b) N LiOH/CH_3OH; c) H_2N-O-SO_3H, HCO_2H, reflux, 3h; d) $Me_3O^+BF_4^-$, CH_2Cl_2; e) NH_4Cl, CH_3OH; f) (t-butylOCO)$_2$O, DMAP, THF;

g) Li hexamethyldisilazide, THF, PhSeCl; h) 30% H_2O_2, THF; i) 4N HCl, HOAc.

Scheme 15:
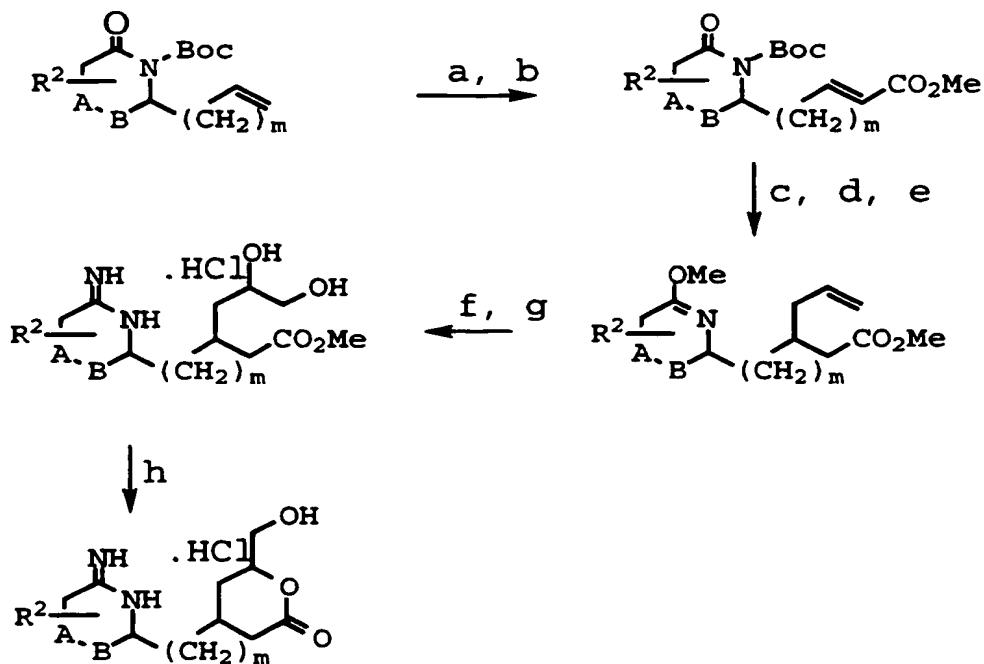
a) O_3 / Ph_3P;   b) $Ph_3P=CH-CO_2CH_3$;   c) $(allyl)_2CuLi$

d) CF_3CO_2H;   e) $Me_3O^+BF_4^-$, CH_2Cl_2;   f) OsO_4, NMO;

g) NH_4Cl, MeOH;   h) dilute acid, warm

Scheme 16:
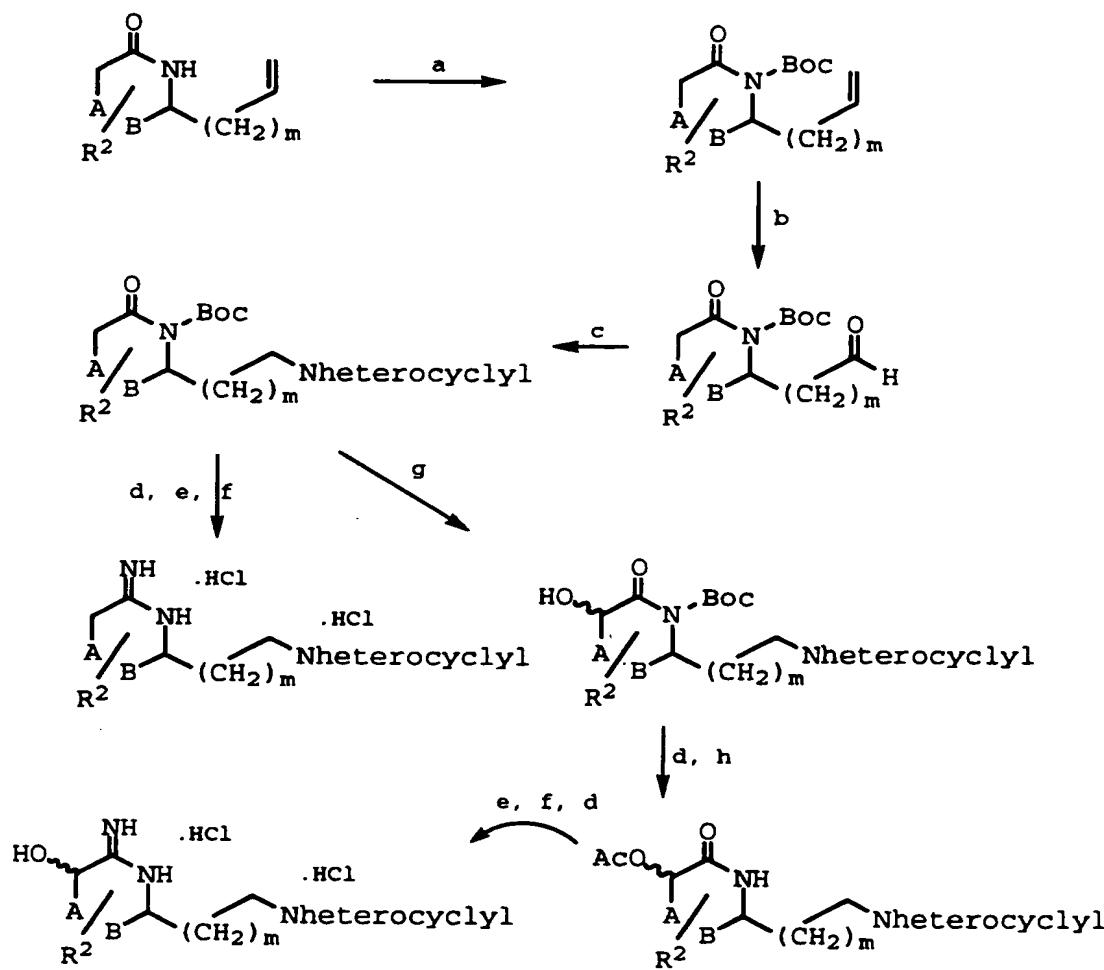
a) di-t-butyl dicarbonate, DMAP, THF ;   b) O_3;   c) HNheterocyclyl = heterocyclyl containing NH as part of ring, H_2, Pd catalyst ;   d) HCl, MeOH;   e) Et_3O^+ BF_4^-, CH_2Cl_2;   f) NH_4Cl, MeOH;   g) organo Li base, TMS_2O_2;   h) Ac_2O, pyridine

Scheme 17
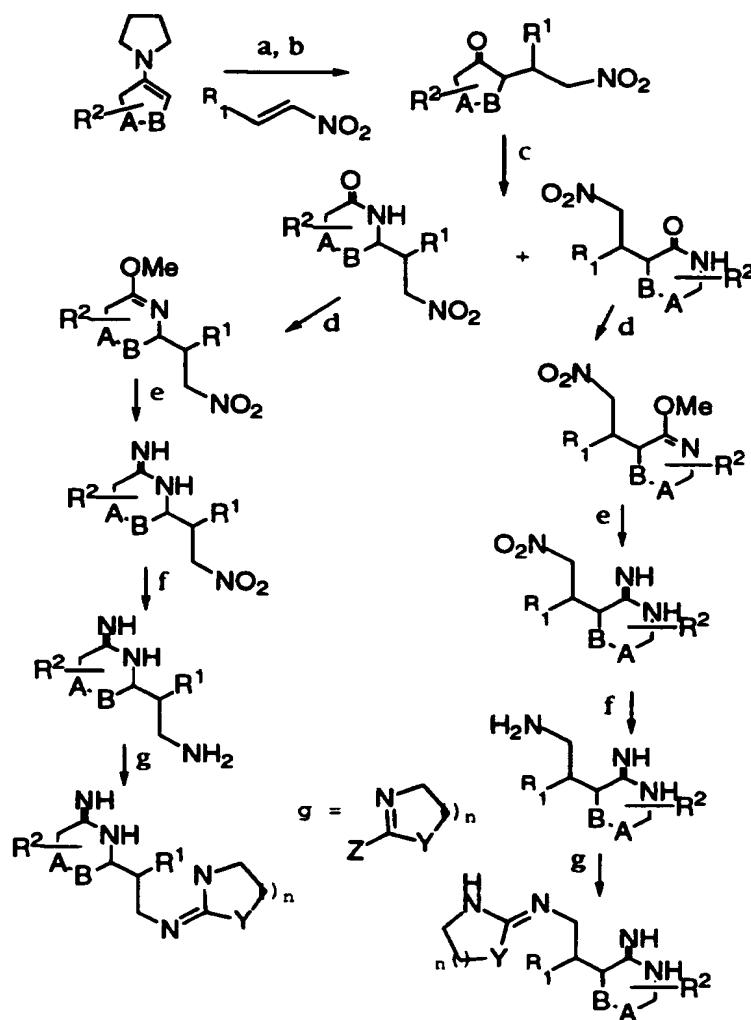
a) 1,4-dioxane; b) H3O+; c) Beckmann Rearrangement; d) Me3O+BF4−; e) NH3; f) catalytic hydrogenation; g) see structure (Z = leaving group; Y = CH2, N, O, S) wherein "n" has a value within 1-4.
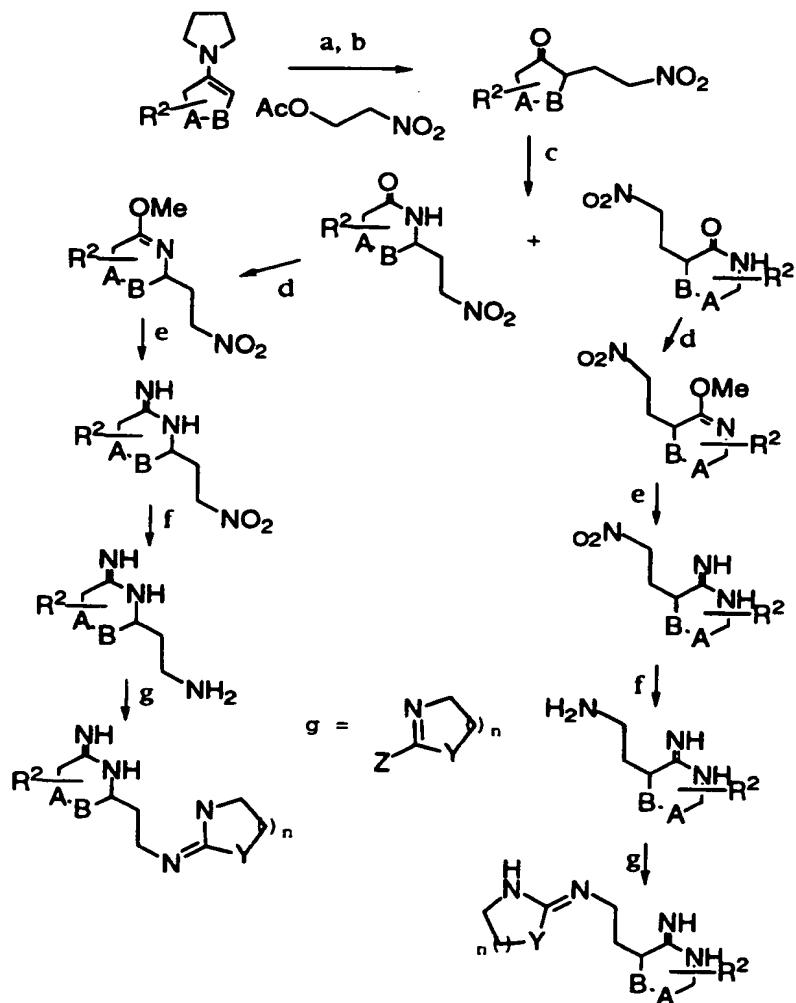
Scheme 18

5   a) 1,4-dioxane; b) H_3O^+; c) Beckmann Rearrangement; d)
     $Me_3O^+BF_4^-$; e) NH_3; f) catalytic hydrogenation; g) see
     structure (Z = leaving group; Y = CH_2, N, O, S) wherein
     "n' has a value within 1-4.

Scheme 19

(from Scheme 17)
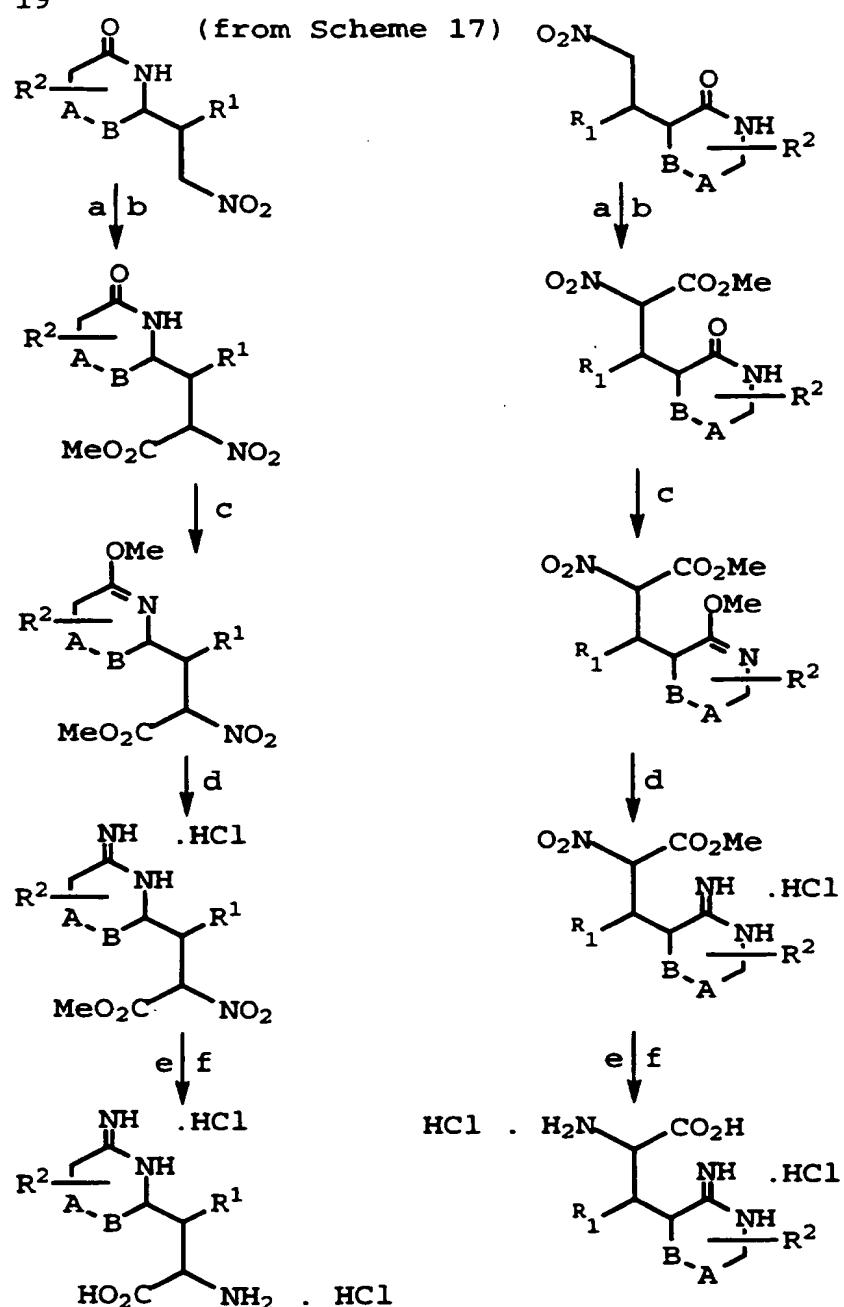
5   a) TBDMSCl, Et$_3$N; b) LiHMDS, ClCO$_2$Me; c) Me$_3$O$^+$BF$_4^-$; d) NH$_4$Cl, MeOH; e) catalytic hydrogenation; f) H$_3$O$^+$.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent.
5   Therefore the following preferred specific embodiments are to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever.

10 All experiments were performed under either dry nitrogen or argon. All solvents and reagents were used without further purification unless otherwise noted. The routine work-up of the reactions involved the addition of the reaction mixture to a mixture of either neutral,
15 or acidic, or basic aqueous solutions and organic solvent. The aqueous layer was extracted n times (x) with the indicated organic solvent. The combined organic extracts were washed n times (x) with the indicated aqueous solutions, dried over anhydrous Na_2SO_4,
20 filtered, concentrated in vacuo, and purified as indicated. Separations by column chromatography were achieved with conditions described by Still. (Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatograhic Technique for Preparative Separation with Moderate Resolution. J.
25 Org. Chem., **1978**, 43, 2923-2925.) The hydrochloride salts were made from 1N HCl, HCl in ethanol (EtOH), 2 N in MeOH, or 6 N HCl in dioxane. Thin layer chromatograms were run on 0.25 mm EM precoated plates of silica gel 60 F254. High performance liquid
30 chromatograms (HPLC) were obtained from C-8 or C-18 reverse phase columns which were obtained from several vendors. Analytical samples were dried in an Abderhalden apparatus at either 56°C or 78°C. ^{1}H NMR spectra were obtained from either General Electric QE-
35 300 or Varian VXR 400 MHz spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR were obtained from a Varian spectrometer at 125.8 MHz with tetramethylsilane as an internal standard.

Example 1

2-(phenylmethyl)cyclohexanone, oxime
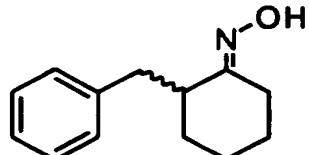
A sample of 2-benzylcyclohexanone (Aldrich, 9.3 g, 49.7 mmol) was combined with hydroxylamine hydrochloride (NH$_2$OH · HCl, 4.8 g, 69.6 mmol) and sodium acetate (NaOAc, 7.3 g, 89.5 mmol) in a mixture of ethanol (EtOH, 90 mL) and water (90 mL). This mixture was refluxed for 15 h under a nitrogen atmosphere. After the reaction was cooled to room temperature, all solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (EtOAc) and water and the organic phase was washed with 1 x 75 mL of saturated NaCl (brine), dried over Na$_2$SO$_4$, and stripped of all solvent under reduced pressure. This provided 9.7 g (97%) of the title compound as a cream colored solid. This material showed a retention time of 17.3 min (100% purity by peak area integration) on a Shimadzu GC-14A gas chromatograph (GC) with a 0.25 mm x 25 M methyl, 5% phenylsilicone column. Under identical conditions, the starting ketone had a retention time of 14.9 min. The NMR and IR spectra of the product were consistent with the assigned structure.

Example 2

hexahydro-7-(phenylmethyl)-2H-azepin-2-one, mixture with
hexahydro-3-(phenylmethyl)-2H-azepin-2-one

Isomer-A   Isomer-B
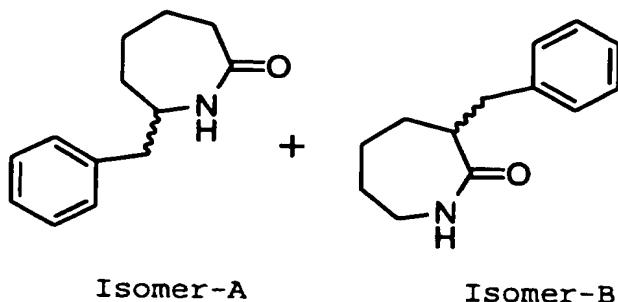
A 2.7 g (13.5 mmol) sample of the title material of Example
1 was added to a dropping funnel containing 2.4 mL of 80%
H_2SO_4. After using a stirring rod to obtain a turbid
solution, this mixture was added dropwise (30 min) to 1 mL
of 80% H_2SO_4 stirred magnetically and maintained at 120 °C
with an external oil bath. Within 5 minutes of the start of
addition an exotherm was noted and the temperature of the
reaction rose to 150 °C before cooling again to 120 °C. Ten
minutes after the addition was complete, the flask was
removed from the bath and allowed to cool to room
temperature. The product mixture was diluted with water (20
mL) and brought to pH 6 with concentrated NH_4OH. This
solution was further diluted with 75 mL of water and
extracted with 2 x 35 mL of CH_2Cl_2. The combined organic
phase was washed with 1 x 35 mL of brine, dried (Na_2SO_4),
filtered, and stripped of all solvent under reduced
pressure. The crude solid (980 mg, 36%) was separated into
its title Isomer-A and Isomer-B components by column
chromatography. Under conditions identical to that
described in Example 1, the Isomer-A and Isomer-B components
had GC retention times of 20.7 and 17.2 minutes
respectively. The NMR and IR spectra of the products were
consistent with their assigned structures.

The Isomer-A material (1.1 g) was chromatographed on a
Chiralpak AD column eluting with 3% isopropanol (IPA)/hexane
to yield 275 mg (50%) of the (+)Isomer-A enantiomer and 254
mg (46%) of the (-)Isomer-A enantiomer. The NMR and IR
5 spectrum of these two compounds were identical in all
respects to that of racemic Isomer-A.

(+)Isomer-A enantiomer:
$[a]_D$ (1.0, CHCl$_3$) = +16.4 ± 3.9
10 Elemental analysis: C$_{13}$H$_{17}$NO (MW = 203.28)

	C	H	N
Calculated:	76.81	8.43	6.89
Found:	76.55	8.69	6.63

15

(-)Isomer-A enantiomer:
$[a]_D$ (1.0, CHCl$_3$) = -13.5 ± 2.7
Elemental analysis: C$_{13}$H$_{17}$NO (MW = 203.28)

20
	C	H	N
Calculated:	76.81	8.43	6.89
Found:	76.53	8.50	6.61

25   Example 3

4,5,6,7-tetrahydro-2-methoxy-7-(phenylmethyl)-2H-azepine
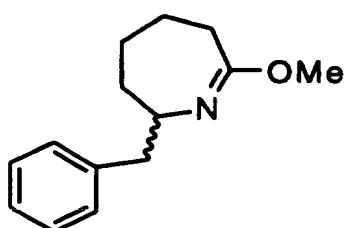
30

To a magnetically stirred slurry of trimethyloxonium
tetrafluoroborate (Lancaster, 0.30 g, 2.0 mmol) and 3A
molecular sieves (2 g) in CH$_2$Cl$_2$ (15 mL) under argon (Ar)
was added the Isomer-A product of Example 2 (0.31 g, 1.5

mmol). This mixture was stirred at room temperature for 3
days before it was diluted with 10 mL of CH_2Cl_2 and
partitioned between 40 mL of saturated $KHCO_3$ and 50 mL of
EtOAc. The organic phase was separated, dried over Na_2SO_4,
5   filtered, and stripped of all solvent under reduced pressure
to provide the crude title product as a pale yellow oil.
This material was chromatographed on Merck silica gel using
conditions describd by W. T. Still *J. Org. Chem.* **1978**, 43,
2923-2925 eluting with EtOAc/n-hexane (1:1). The title pale
10 yellow liquid product (308 mg, 93%) had a GC retention time
of 15.5 min (100%) under the conditions of Example 1 and NMR
and IR spectra consistent with the indicated product.

15   Example 4

4,5,6,7-tetrahydro-2-methoxy-3-(phenylmethyl)-2H-azepine

20
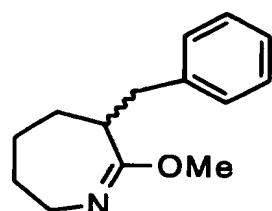
The Isomer-B product of Example 2 is reacted with
trimethyloxonium tetrafluoroborate by the method of Example
3 to produce the title material.

Example 5

hexahydro-7-(phenylmethyl)-2H-azepin-2-imine,
monohydrochloride
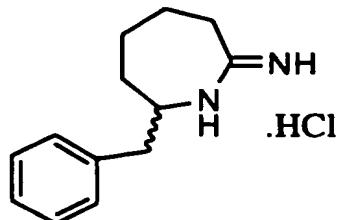
The title product of Example 3 (0.30 g, 1.4 mmol) and 0.06 g
(1.1 mmol) of ammonium chloride (NH4Cl) were refluxed in 13
mL of methanol (MeOH) under a nitrogen atmosphere for 19 h.
After cooling the reaction to room temperature, it was
filtered, stripped of all solvent under reduced pressure,
and partitioned between 15 mL of water and 7 mL of CH_2Cl_2.
The organic and aqueous phases were separated and the
aqueous phase was washed with a 25 mL portion of EtOAc
before it was lyophilized to provide 0.24 g (92%) of the
white solid title material.

HRMS (EI) calcd for $C_{13}H_{18}N_2$ m/e 202.147, found m/e 202.147.
^{1}H NMR(CD3OD): d 7.20-7.35 (m, 5H), 3.96 (m, 1H), 2.99 (dd,
1H, J=14.8 Hz), 2.89 (dd, 1H, J=14.8 Hz), 2.82 (m, 1H), 2.64
(m, 1H) 2.05-1.86 (m, 3H), 1.71-1.36 (m, 3H).

Elemental analysis: $C_{13}H_{18}N_2$ · HCl · 0.15 H_2O (MW = 241.46)

	C	H	N	Cl
Calculated:	64.67	8.06	11.60	14.68
Found:	64.86	8.45	11.54	14.60

Example 6

hexahydro-3-(phenylmethyl)-2H-azepin-2-imine,
monohydrochloride

5
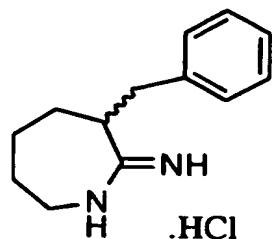
The title product of Example 4 in MeOH is reacted with
ammonium chloride by the method of Example 5 to generate the
10   title material.


Example 7

15   7-(cyclohexylmethyl)hexahydro-2H-azepin-2-one
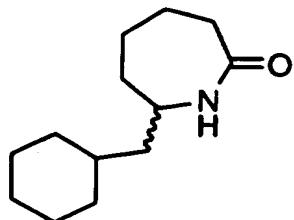
The Isomer-A title product of Example 2 (0.80 g, 3.9 mmol)
20   dissolved in MeOH was placed in a standard Parr
hydrogenation shaker flask along with 5% Rh/C. The reaction
mixture was shaken under an H_2 pressure of 60 psi at 60 °C
for 22 hr. All solvent was then removed under reduced
pressure. The residue was then dissolved in CH_2Cl_2 and this
25   solution was filtered and stripped of all solvent to yield
875 mg of the title material. The colorless semi-solid
title product had a GC retention time of 15.5 min (100%)
under the conditions of Example 1 and NMR and IR spectra
consistent with the title product.

Example 8

5   2-(cyclohexylmethyl)-3,4,5,6-tetrahydro-7-methoxy-2H-azepine
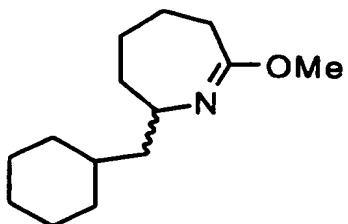
The title product of Example 7 (0.87 g, 4.2 mmol) was
10   reacted with trimethyloxonium tetrafluoroborate (0.80 g, 5.4
mmol) by the method of Example 3 to yield 0.76 g (82%) of
the title material. The pale yellow oil title product had a
GC retention time of 14.9 min (100%) under the conditions of
Example 1 and NMR and IR spectra consistent with the title
15   product.

Example 9

20   7-(cyclohexylmethyl)hexahydro-2H-azepin-2-imine,
monohydrochloride
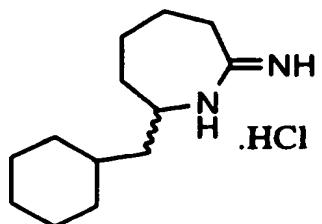
25   The product of Example 8 (0.76 g, 3.4 mmol) in 20 mL of MeOH
was reacted with ammonium chloride (144 mg, 2.7 mmol) by the
method of Example 5 to yield 258 mg (30.4%) of the title
material.

HRMS (EI) calcd for $C_{13}H_{24}N_2$ m/e 208.194, found m/e 208.195.
^{1}H NMR(CD$_3$OD): d 3.70 (m, 1H), 2.82 (m, 1H), 2.61 (m, 1H),
2.06-1.93 (m, 2H), 1.86-1.62 (m, 7H), 1.62.-1.13 (m, 8H).

5   Elemental analysis: $C_{13}H_{24}N_2 \cdot HCl \cdot 0.33\ H_2O$ (MW = 250.81)

	C	H	N	Cl
Calculated:	62.27	10.31	11.17	14.14.
Found:	62.23	10.09	10.83	13.52

10

Example 10

3-(cyclohexylmethyl)hexahydro-2H-azepin-2-one,
15   monohydrochloride
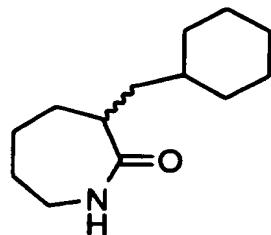
The Isomer-B title product of Example 2 is converted to the
20   title material by the method of Example 7.

Example 11

6-(cyclohexylmethyl)-3,4,5,6-tetrahydro-7-methoxy-2H-azepine

5
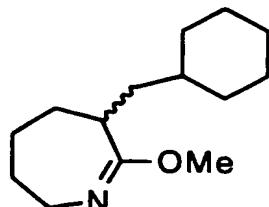
The product of Example 10 is reacted with trimethyloxonium
tetrafluoroborate by the method of Example 3 to produce the
title material.

10

Example 12

3-(cyclohexylmethyl)hexahydro-2H-azepin-2-imine,
15   monohydrochloride
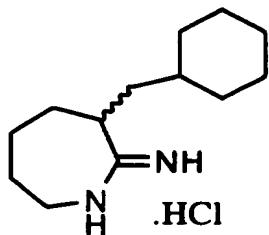
The title product of Example 11 in MeOH is reacted with
20   ammonium chloride by the method of Example 5 to generate the
title material.

Example 13

(+)-3,4,5,6-tetrahydro-7-methoxy-2-(phenylmethyl)-2H-azepine

5
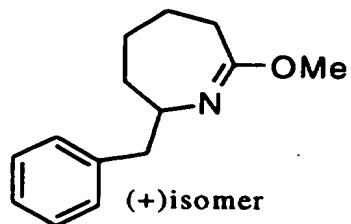
(+)isomer

The (+)Isomer-A enantiomer product of Example 2 (0.24 g, 1.2 mmol) was reacted with trimethyloxonium tetrafluoroborate

10 (0.23 g, 1.6 mmol) by the method of Example 3 to yield 0.25 g (95%) of the title material. The pale yellow oil title product had a GC retention time of 15.4 min (100%) under the conditions of Example 1 and NMR and IR spectra were identical to the title products of Examples 3 and 15.

15

Example 14

(+)-hexahydro-7-(phenylmethyl)-2H-azepin-2-imine,
20 monohydrochloride

(+)isomer
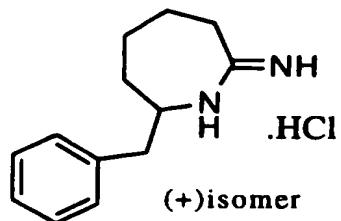
The product of Example 13 (0.25 g, 1.1 mmol) in 19 mL of
25 MeOH was reacted with ammonium chloride (50 mg, 0.93 mmol) by the method of Example 5 to yield 200 mg (88%) of the title material. The NMR and IR spectra of the title compound were identical to that of the title products of Examples 5 and 16.

HRMS (EI) calcd for $C_{13}H_{18}N_2$ m/e 202.147, found m/e 202.147.
$[a]_D$ (0.095, CHCl$_3$) = +35.6 ± 2.8

Elemental analysis: $C_{13}H_{24}N_2$ · 0.95 HCl · 0.45 H$_2$O (MW = 245.04)

	C	H	N	Cl
Calculated:	63.72	8.17	11.43	13.74
Found:	64.05	8.70	11.15	13.91

Example 15

(-)-3,4,5,6-tetrahydro-7-methoxy-2-(phenylmethyl)-2H-azepine
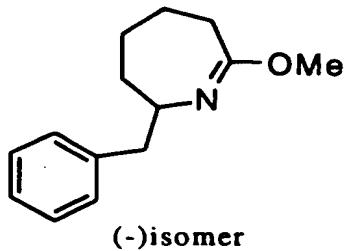
(-)isomer

The (-)Isomer-A enantiomer product of Example 2 (0.23 g, 1.1 mmol) was reacted with trimethyloxonium tetrafluoroborate (0.21 g, 1.4 mmol) by the method of Example 3 to yield 0.21 g (88%) of the title material. The pale yellow oil title product had a GC retention time of 15.4 min (100%) under the conditions of Example 1 and NMR and IR spectra were identical to the title products of Examples 3 and 13.

Example 16

(-)-hexahydro-7-(phenylmethyl)-2H-azepin-2-imine, monohydrochloride

5

(-)isomer
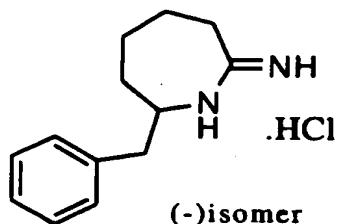
The product of Example 15 (0.21 g, 1.0 mmol) in 18 mL of MeOH was reacted with ammonium chloride (43 mg, 0.80 mmol)

10 by the method of Example 5 to yield 173 mg (89%) of the title material. The NMR and IR spectra of the title compound were identical to that of the title products of Examples 5 and 14.

15 HRMS (EI) calcd for $C_{13}H_{18}N_2$ m/e 202.147, found m/e 202.147.
$[a]_D$ (0.149, CHCl$_3$) = -35.6 $\pm$ 2.8
Elemental analysis: $C_{13}H_{24}N_2 \cdot HCl \cdot 0.2\ H_2O$ (MW = 242.36)

|	C	H	N	Cl
20 Calculated:	64.43	8.07	11.56	14.63
Found:	64.43	8.31	11.15	14.88

Example 17

2-(2-propenyl)cyclohexanone, oxime
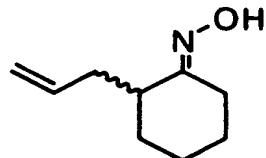
A sample of 2-allylcyclohexanone (Frinton, 2.0 g, 14.5 mmol) was converted to the title compound by the method of Example 1 using 1.5 g (21.7 mmol) of hydroxylamine hydrochloride and 2.0 g (24.6 mmol) of NaOAc in a mixture of 25 mL of EtOH and 25 mL of water. The procedure produced 2.6 g of the crude title compound.

Example 18

hexahydro-3-(2-propenyl)-2H-azepin-2-one, mixture with hexahydro-7-(2-propenyl)-2H-azepin-2-one
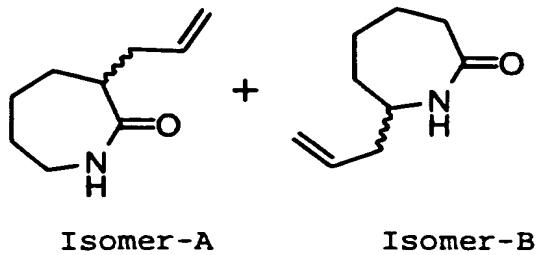

Isomer-A   Isomer-B

The title product of Example 17 (2.0 g, 13.0 mmol) in 15 mL of acetone containing 1N NaOH (14.3 mL, 52.4 mmol) was reacted with benzene sulfonylchloride (2.3 g, 13.1 mmol) by the method described in Example 67. The crude reaction mixture was separated into its Isomer-A and Isomer-B components by silica gel chromatography.

Example 19

hexahydro-7-[(oxiran-2-yl)methyl]-2H-azepin-2-one

5
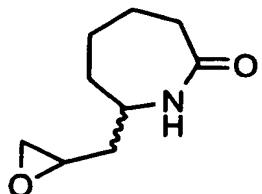
The title product isomer B of Example 18 (2.99 g, 19.5 mmol) in 150 mL of CH_2Cl_2 was refluxed with m-chloroperbenzoic acid (MCPBA, 5.05 g, 29.3 mmol) for 3
10   hr. After stirring at room temperature overnight, an additional 1.0 g (5.8 mmol) of MCPBA was added and the reaction reheated to reflux for an additional 6 hr. The solvent was removed and the residue was dissolved in EtOAc (150 mL). After this solution was washed 3 x 50 mL
15   of saturated $NaHCO_3$ and dried (Na_2SO_4), all solvent was removed to provided the crude desired product. Purification via flash column chromatography using 100% EtOAc and deactivated silica gel yielded 2.25 g (68%) of the title compound.
20

Example 20

3,4,5,6-tetrahydro-7-methoxy-2-[(oxiran-2-yl)methyl]-2H-
25   azepine
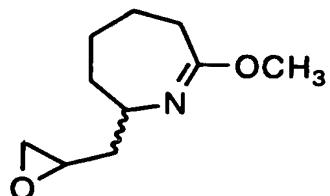
The product of Example 19 (2.0 g, 13 mmol) was reacted
30   with trimethyloxonium tetrafluoroborate (2.49 g, 16.8

mmol) in CH_2Cl_2 (80 mL) by the method of Example 3 to produce 1.8 g (83 %) of the title material following chromatography.

5

Example 21

hexahydro-7-[(oxiran-2-yl)methyl]-2H-azepin-2-imine, monohydrochloride

10
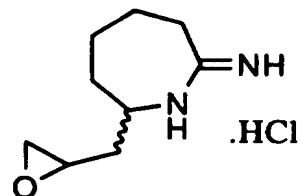
The product of Example 20 in MeOH was reacted with ammonium chloride by the method of Example 5 to yield the
15   title material.

Example 22

hexahydro-7-[(2-hydroxy-3-(2-hydroxyphenoxy)propyl]-2H-azepin-2-one

5
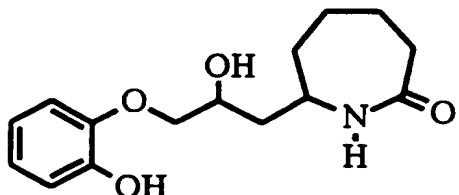
Sodium hydride (52.4% in mineral oil, 66.5 mmol, 3.05 g) is washed with hexane in a 500 mL flask. The hexane-

10   mineral oil is decanted, and DMF (35 mL) is added. A dropping funnel is fitted onto the flask, with nitrogen flow maintained through the reaction system. 1,2-Dihydroxybenzene (63.6 mmol, 7.0 g) dissolved in DMF (150 mL) is added CAREFULLY dropwise to the stirring mixture.

15   When the addition is complete, the mixture is allowed to stir at room temperature for one hour. The title compound of Example 19 (58 mmol) is dissolved in DMF (100 mL) and added quickly to the reaction mixture. The stirring mixture is immersed in a 75 °C oil bath, and

20   allowed to react for 24 h. The mixture is removed from the oil bath, allowed to come to room temperature, and poured into 150 mL 0.5M KHSO4 solution. This mixture is diluted with water to 500 mL, and extracted thrice with 150 mL portions of CH2Cl2. The organic fractions are

25   combined, dried (MgSO4), filtered, and stripped at reduced pressure. The residue is purified by silica column chromatography to give the title compound.

Example 23

7-[(1,4-benzodioxan-2-yl)methyl]hexahydro-2H-azepin-2-one
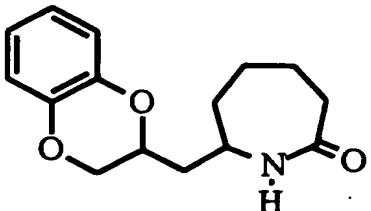
5

A 1000 mL three-necked round bottom flask fitted with a
magnetic stirrer, thermometer, dropping funnel, and Y-
tube (nitrogen inlet, drying tube outlet) is charged with
10   the title compound from Example 22 (21.6 mmol),
triphenylphosphine (5.67 g, 21.6 mmol), and THF (300 mL).
The temperature is reduced to 2 °C (ice bath), and
diethyl azodicarboxylate (DEAD, 3.77 g, 3.4 mL, 21.6
mmol) in 50 mL THF is added dropwise, keeping the
15   reaction temperature at or below 4 °C. After the
addition is completed, the reaction is stirred a further
45 min in the ice bath; the cold bath is removed and the
mixture is allowed to stir at room temperature overnight.
The reaction mixture is then stripped in vacuo to a
20   residue which is applied to a silica gel column for
purification with hexane/ethyl acetate eluents giving the
title compound.

25   Example 24

2-[(1,4-benzodioxan-2-yl)methyl]-3,4,5,6-tetrahydro-7-
methoxy-2H-azepine

30
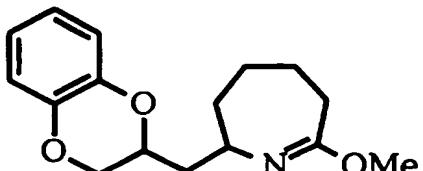
The title compound of Example 23 is treated by the
method described in Example 3 to yield the present
title compound.

Example 25

7-[(1,4-benzodioxan-2-yl)methyl]hexahydro-2H-azepin-2-
imine, monohydrochloride
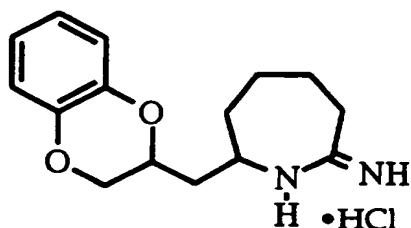
The title compound of Example 24 is treated by the
method described in Example 5 to yield the present title
compound.

Example 26

3,4,5,6-tetrahydro-7-methoxy-2-[2-methoxy-3-(2-
methoxyphenoxy)propyl]-2H-azepine
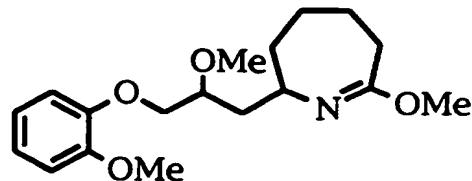
The title compound of Example 22 is treated by the
method described in Example 3 to yield the present title
compound.

Example 27

hexahydro-7-[2-methoxy-3-(2-methoxyphenoxy)propyl]-2H-
azepin-2-imine, monohydrochloride

5
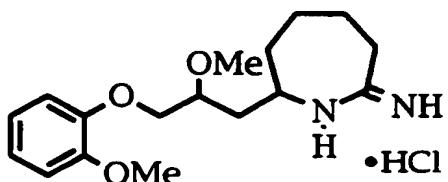
The title compound of Example 26 is treated by the
method described in Example 5 to yield the present title
10   compound.

Example 28

15   7-[2-acetyloxy-3-(2-acetyloxyphenoxy)propyl]hexahydro-2H-
azepin-2-one
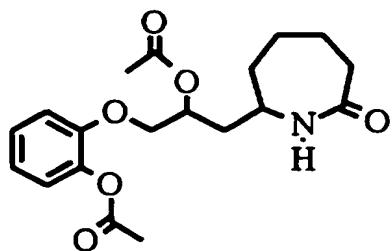
20   The title compound of Example 22 (20 mmol) is dissolved
in 100 mL CH$_2$Cl$_2$ and cooled to -5 °C (ice-methanol bath).
The solution is protected from moisture and 10 mL dry
pyridine is added. A solution of 50 mmol acetic
anhydride in 20 mL CH$_2$Cl$_2$ is slowly added, keeping the
25   reaction temperature at or below 0 °C. The mixture is
allowed to stir an additional 2 hr, and is then stripped
in vacuo to a residue. This residue is partitioned
between 0.1 M KHSO$_4$ and ether. The aqueous phase is
washed with ether, the organic phases are combined, dried

(MgSO4), filtered and stripped in vacuo to give the title compound.

Example 29

a-[(2-acetyloxyphenoxy)methyl]-3,4,5,6-tetrahydro-7-methoxy-2H-azepine-2-ethanol acetate(ester)
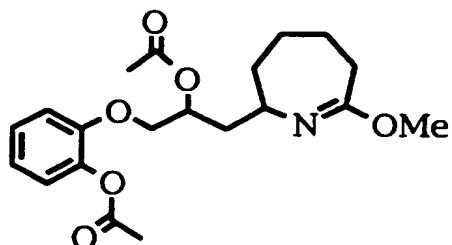
The title compound of Example 28 is treated by the method described in Example 3 to yield the present title compound.

Example 30

hexahydro-a-[(2-hydroxyphenoxy)methyl]-7-imino-1H-azepine-2-ethanol, monohydrochloride
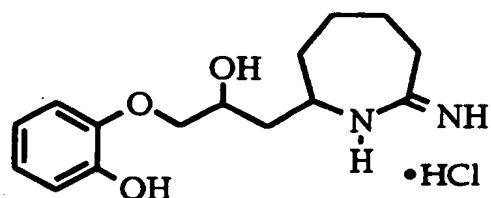

The title compound of Example 29 is treated by the method described in Example 5 to yield the partially acetylated present title compound. The acetyl groups are removed with refluxing (1 hr) 0.5 N HCl, followed by in vacuo concentration to one third volume. The resulting aqueous solution is lyophilized to give title compound.

Example 31

a-[(2-acetyloxyphenoxy)methyl]hexahydro-7-imino-1H-
azepine-2-ethanol acetate(ester), monohydrochloride

5
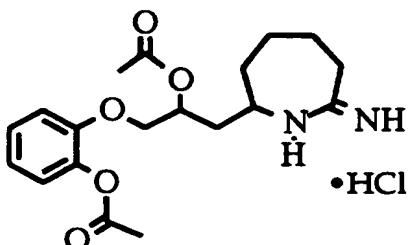
The dried title compound of Example 30 is treated with a
three-fold excess of acetyl chloride in CH_2Cl_2, followed

10   by stripping in vacuo. The resulting residue is
dissolved in water and lyophilized to give the title
compound.

15   Example 32

hexahydro-7-(3-phenyl-2-propenyl)-2H-azepin-2-one
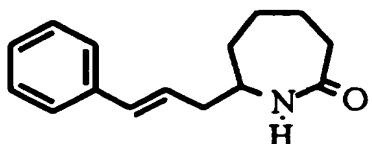
20

A mixture of palladium acetate (Johnson Matthey, 65 mg,
0.29 mmol), tri-o-tolylphosphine (Aldrich, 176 mg, 0.6
mmol), bromobenzene (Aldrich, 2.50 g, 16.0 mmol), and
triethylamine (Aldrich, 1.62 g, 16 mmol) was refluxed

25   under nitrogen for 30 minutes. After cooling this
mixture to room temperature, the isomer B of the title
material of Example 18 (2.2 g, 14.5 mmol) in 6 mL of
acetonitrile was added to the reaction mixture. The
reaction was refluxed for 24 hrs., cooled to room

30   temperature, and stripped of all solvent under reduced
pressure. The residue was partitioned between saturated

NaHCO3 and EtOAc and the organic was dried (Na2SO4),
filtered and concentrated to the crude product. This
material was chromatographed (HPLC) on silica gel eluting
with acetone/hexane (1:1) to give 1.06 g (32%) of the
5   title material.

Elemental analysis: $C_{15}H_{19}NO$ (MW = 229.32)

	C	H	N
10 Calculated:	78.57	8.35	6.11
Found:	78.14	8.31	5.89

Example 33

15

3,4,5,6-tetrahydro-7-methoxy-2-(3-phenyl-2-propenyl)-2H-
azepine

20
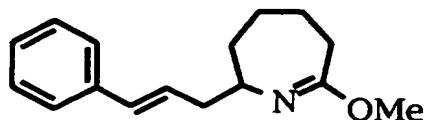
The title material of Example 32 (0.50 g, 2.2 mmol) in
CH2Cl2 (15 mL) and in the presence of 3A molecular sieves
(1.0 g) was reacted with trimethyloxonium tetrafluoroborate
(0.39 g, 2.6 mmol) by the method of Example 3 to produce
25   0.53 g (99%) of the title material.

Example 34

hexahydro-7-(3-phenyl-2-propenyl)-2H-azepin-2-imine,
monohydrochloride

5
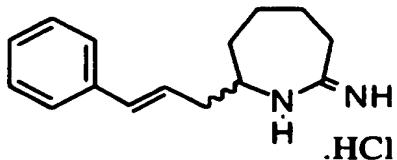
The product of Example 33 (0.50 g, 2.05 mmol) in 18 mL of
MeOH was reacted with ammonium chloride (144 mg, 2.7 mmol)

10   by the method of Example 5 to yield 258 mg (30%) of the
title material.

HRMS (EI) calcd for $C_{15}H_{20}N_2$ m/e 228.163, found m/e 228.163.
^{1}H NMR(CD$_3$OD): d 7.40-7.17 (m, 5H), 6.59 (d, 1H, J=16 Hz),

15   6.26 (dt, 1H, J=16, 7 Hz), 3.80 (m, 1H), 2.80 (td, 1H, J=15,
2 Hz), 2.55 (m, 2H), 2.64 (dd, 1H, J=15, 6 Hz), 2.03-1.92
(m, 3H), 1.70 (m, 1H), 1.55-1.38 (m, 2H).

Elemental analysis: $C_{15}H_{20}N_2$ · HCl · 0.8 H_2O · 0.05 NH$_4$Cl (MW

20   = 281.88)

	C	H	N	Cl
Calculated:	63.91	8.15	10.19	13.21
Found:	63.86	8.10	9.97	13.42

25

Example 35

hexahydro-7-(3-phenylpropyl)-2H-azepin-2-one

30
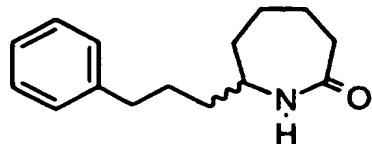
The title material of Example 32 (0.46 g, 2.0 mmol) in MeOH and 4% Pd on carbon (0.10 g) were combined in a standard Parr apparatus (125 mL bottle). The hydrogenation was carried out at room temperature under a
5 H_2 pressure of 5 psi for 1 hr. All solvent was then removed under reduced pressure to yield 0.50 g (99%) of the title material as a white semi-solid.

Elemental analysis: $C_{15}H_{21}NO$ (MW = 231.33)
10

	C	H	N
Calculated:	77.28	9.17	6.01
Found:	77.15	8.97	5.89

15   Example 36

3,4,5,6-tetrahydro-7-methoxy-2-(3-phenylpropyl)-2H-azepine

20
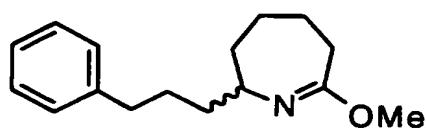
The title material of Example 35 (0.47 g, 2.0 mmol) in CH_2Cl_2 (10 mL) and in the presence of 3A molecular sieves (1.0 g) was reacted with trimethyloxonium tetrafluoroborate
25 (0.35 g, 2.4 mmol) by the method of Example 3 to produce 0.42 g (87%) of the title material as a pale yellow oil.

Example 37

hexahydro-7-(3-phenylpropyl)-2H-azepin-2-imine,
monohydrochloride
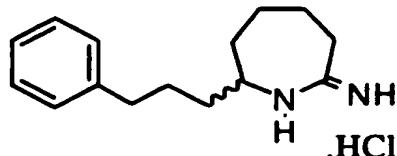
The product of Example 36 (0.41 g, 1.65 mmol) in 18 mL of
EtOH was reacted with ammonium chloride (75 mg, 1.4 mmol) by
the method of Example 5 to yield 195 mg (63%) of the title
material.

HRMS (EI) calcd for $C_{15}H_{22}N_2$ m/e 230.178, found m/e 230.178.
^{1}H NMR(CD3OD): d 7.28-7.13 (m, 5H), 3.57 (m, 1H), 2.73 (ddd,
1H, J=15,12, 2 Hz), 2.67 (t, 2H, J=8 Hz), 2.57 (dd, 1H,
J=15, 7 Hz), 1.96 (m, 2H), 1.85-1.57 (m, 6H), 1.47 (m, 1H),
1.35 (m, 1H).

Elemental analysis: $C_{15}H_{22}N_2 \cdot HCl \cdot 0.25 H_2O$ (MW = 271.32)

	C	H	N	Cl
Calculated:	66.40	8.73	10.32	13.07
Found:	66.31	8.91	10.10	13.06

Example 38

2-[(tetrahydro-2-furanyl)methyl]cyclohexanone
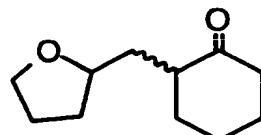
2-carboethoxycyclohexanone (1 mmol), finely powdered
potassium carbonate (2 mmol) , 2-bromomethyltetrahydrofuran

(1.5 mmol), and tetrabutylammonium iodide (10 mg/mmol) are combined in dry DMF (1.25 mL/mmol) and stirred under N2 at 55 to 60 °C for 16 to 18 hours. The room temperature reaction mixture is poured into water and extracted with Et2O and EtOAc. The combined organics are washed with brine, dried, and stripped of all solvent under reduced pressure to provide 2-tetrahydrofuranylmethyl-2-carboethoxycyclohexanone. This material is combined with lithium chloride (5 mmol), water (1.05 mmol) and dimethyl sulfoxide (5 mL/mmol) and the mixture refluxed for approximately 4 hrs. The mixture is poured into water and extracted with Et2O and EtOAc. The combined organics are washed with brine, dried, and stripped of all solvent under reduced pressure to generate the title material.

Example 39

2-[(tetrahydro-2-furanyl)methyl]cyclohexanone, oxime
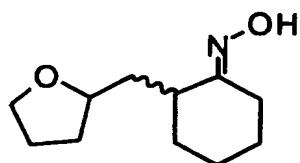
The product of Example 38 is reacted with hydroxylamine hydrochloride and NaOAc in a mixture of EtOH and water, by the method of Example 1 to produce the title material.

Example 40

hexahydro-7-[(tetrahydro-2-furanyl)methyl]-2H-azepin-2-
one, mixture with hexahydro-3-[(2-
5   tetrahydrofuranyl)methyl]-2H-azepin-2-one
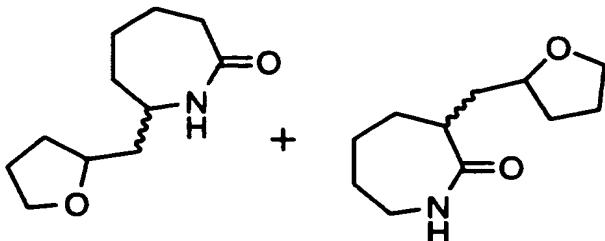
Isomer-A   Isomer-B

10

The product of Example 39 is reacted with 80% H_2SO_4, by the
method of Example 2 to produce the title materials.

15   Example 41

3,4,5,6-tetrahydro-7-methoxy-2-[(tetrahydro-2-
furanyl)methyl]-2H-azepine
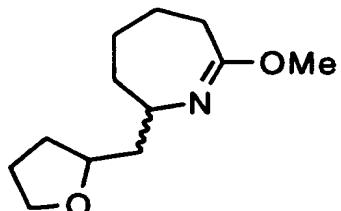
20

The Isomer-A product of Example 40 is reacted with
trimethyloxonium tetrafluoroborate by the method of Example
3 to produce the title material.

25

Example 42

3,4,5,6-tetrahydro-7-methoxy-6-[(tetrahydro-2-
furanyl)methyl]-2H-azepine
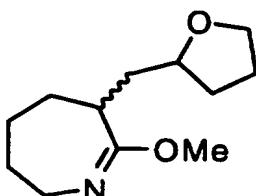
5

The Isomer-B product of Example 40 is reacted with
trimethyloxonium tetrafluoroborate by the method of Example
10   3 to produce the title material.

Example 43

15   hexahydro-7-[(tetrahydro-2-furanyl)methyl]-2H-azepin-2-
imine, monohydrochloride
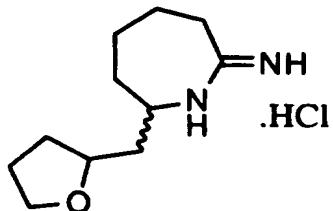
20   The title product of Example 41 in MeOH is reacted with
ammonium chloride by the method of Example 5 to generate the
title material.

Example 44

hexahydro-3-[(tetrahydro-2-furanyl)methyl]-2H-azepin-2-imine, monohydrochloride
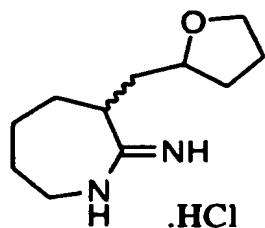

The title product of Example 42 in MeOH is reacted with ammonium chloride by the method of Example 5 to generate the title material.

Example 45

2-[(2-furanyl)methyl]cyclohexanone
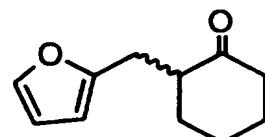
2-carboethoxycyclohexanone, finely powdered potassium carbonate, 2-bromomethyl furan, and tetrabutylammonium iodide are reacted by the method of Example 38 to generate the title material.

Example 46

2-[(2-furanyl)methyl]cyclohexanone, oxime
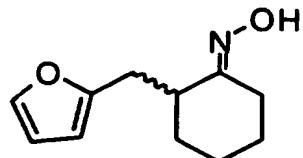
The product of Example 45 is reacted with hydroxylamine hydrochloride and NaOAc in a mixture of EtOH and water, by the method of Example 1 to produce the title material.

Example 47

7-[(2-furanyl)methyl]hexahydro-2H-azepin-2-one, mixture with 3-[(2-furanyl)methyl]hexahydro-2H-azepin-2-one
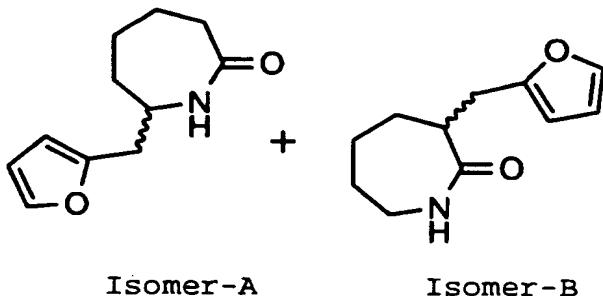
Isomer-A   Isomer-B

The product of Example 46 is reacted with 80% H2SO4, by the method of Example 2 to produce the title materials.

Example 48

2-[(2-furanyl)methyl]-3,4,5,6-tetrahydro-7-methoxy-2H-
azepine
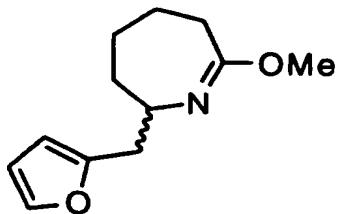
5

The Isomer-A product of Example 47 is reacted with
trimethyloxonium tetrafluoroborate by the method of Example
10   3 to produce the title material.

Example 49

15   6-[(2-furanyl)methyl]-3,4,5,6-tetrahydro-7-methoxy-2H-
azepine
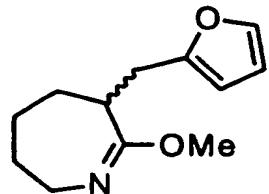
20   The Isomer-B product of Example 47 is reacted with
trimethyloxonium tetrafluoroborate by the method of Example
3 to produce the title material.

Example 50

7-[(2-furanyl)methyl]hexahydro-2H-azepin-2-imine, monohydrochloride
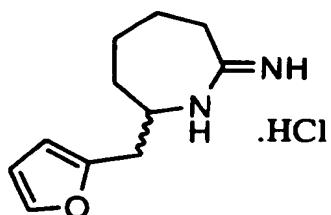
The title product of Example 48 in MeOH is reacted with ammonium chloride by the method of Example 5 to generate the title material.

Example 51

3-[(2-furanyl)methyl]hexahydro-2H-azepin-2-imine, monohydrochloride
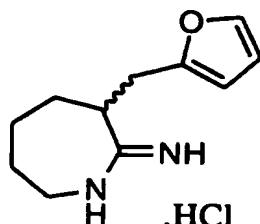

The title product of Example 49 in MeOH is reacted with ammonium chloride by the method of Example 5 to generate the title material.

Example 52

2-[(2-thienyl)methyl]cyclohexanone
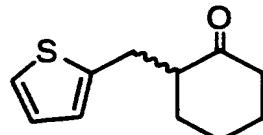
2-carboethoxycyclohexanone, finely powdered potassium carbonate, 2-bromomethyl thiophene, and tetrabutylammonium iodide are reacted by the method of Example 38 to generate the title material.

Example 53

2-[(2-thienyl)methyl]cyclohexanone, oxime
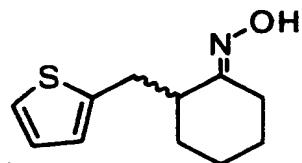
The product of Example 52 is reacted with hydroxylamine hydrochloride and NaOAc in a mixture of EtOH and water, by the method of Example 1 to produce the title material.

Example 54

hexahydro-7-[(2-thienyl)methyl]-2H-azepin-2-one, mixture with hexahydro-3-[(2-thienyl)methyl]-2H-azepin-2-one
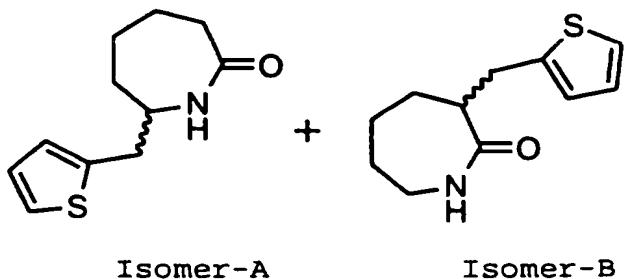
Isomer-A   Isomer-B

The product of Example 53 is reacted with 80% H2SO4, by the method of Example 2 to produce the title materials.

5

Example 55

3,4,5,6-tetrahydro-7-methoxy-2-[(2-thienyl)methyl]-2H-azepine

10
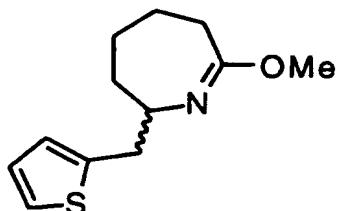
The Isomer-A product of Example 54 is reacted with trimethyloxonium tetrafluoroborate by the method of Example
15 3 to produce the title material.

Example 56

3,4,5,6-tetrahydro-7-methoxy-6-[(2-thienyl)methyl]-2H-
20 azepine
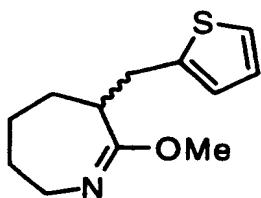
The Isomer-B product of Example 54 is reacted with
25 trimethyloxonium tetrafluoroborate by the method of Example 3 to produce the title material.

Example 57

hexahydro-7-[(2-thienyl)methyl]-2H-azepin-2-imine,
monohydrochloride

5
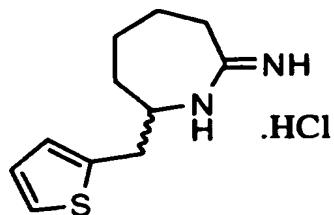
The title product of Example 55 in MeOH is reacted with
ammonium chloride by the method of Example 5 to generate the
10   title material.

Example 58

15   hexahydro-3-[(2-thienyl)methyl]-2H-azepin-2-imine,
monohydrochloride
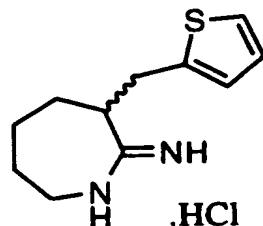
20   The title product of Example 56 in MeOH is reacted with
ammonium chloride by the method of Example 5 to generate the
title material.

Example 59

4-phenyl-2-buten-1-ol
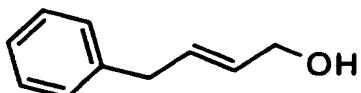
To a -10 °C solution of phenylmagnesium bromide, 3M in ether (68 mL) was added a solution of cupric acetate (5.6 g) and butadiene monoxide (6.43 mL) in THF (200 mL) over 40 min while maintaining the reaction temperature below -5 °C. The reaction was stirred at -10 °C for 1 h, room temperature for 16 h, refluxed for 15 min then cooled to room temperature. Aqueous HCl (10%, 100 mL) was added and the mixture extracted with ethyl acetate. The organic solution was washed with aqueous HCl (10%), NaHCO$_3$ (saturated) and brine (saturated), dried (MgSO$_4$) and concentrated to yield a blue liquid. The residue was chromatographed to yield the title compound (6.3 g, 30%).

Elemental analysis: C$_{10}$H$_{12}$O (MW = 146.21)

	C	H
Calculated:	82.15	8.27
Found:	82.18	8.61

Example 60

2,2,2-trichloro-N-[1-(phenylmethyl)-2-propenyl]acetamide
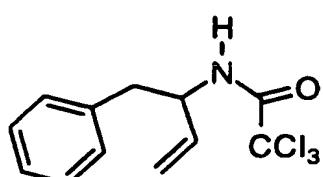
A solution of the product of Example 59 (5.15 g) in ether
(20 mL) was added to a suspension of NaH (0.1 equivalent)
in ether (40 mL). The solution was cooled to -15 °C and
treated with trichloroacetonitrile (3.6 mL) over 30 min,
the solution was stirred at room temperature for 1 h,
treated with a solution of pentane (100 mL) and methanol
(0.4 mL), filtered and concentrated. The residue was
then dissolved in xylene (500 mL) and refluxed for 12 h.
Concentration of the reaction mixture followed by
chromatography afforded the title material (6.9 g, 69%).

Elemental analysis: $C_{12}H_{12}NOCl_3$ (MW = 292.59)

	C	H	N
Calculated:	49.26	4.13	4.79
Found:	48.88	4.07	4.76

Example 61

trans-3,3-dichloro-4-(chloromethyl)-5-
(phenylmethyl)pyrrolidin-2-one
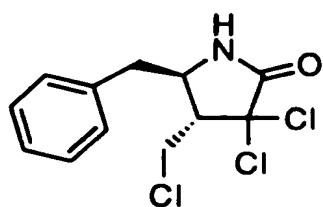
A solution of the product of Example 60 (2.7 g, 9.3 mmol)
in xylene (100 mL) was reacted with bis-
triphenylphosphine-ruthenium dichloride (300 mg) and
refluxed for 8 h. Concentration of the reaction mixture
followed by chromatography afforded the title material
(1.5 g, 55%).

Example 62

trans-4-methyl-5-(phenylmethyl)pyrrolidin-2-one

5
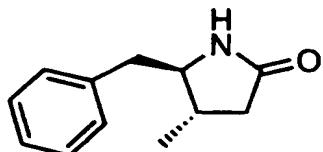
A solution of the product of Example 61 (1.3 g),
tributyltin hydride (3.85 g) and AIBN (16 mg) in toluene
(50 mL) was refluxed for 4 hours. The reaction mixture
10 was treated with a solution of KF (20%, 40 mL) and ethyl
acetate (100 mL), filtered, concentrated and
chromatographed to yield the title material (270 mg).

Elemental analysis: $C_{12}H_{15}NO \cdot 0.1\ CH_3CO_2C_2H_5$ (MW = 198.06)
15

	C	H	N
Calculated:	75.19	8.04	7.07
Found:	74.84	7.92	7.15

20

Example 63

trans-3,4-dihydro-5-methoxy-3-methyl-2-(phenylmethyl)-2H-
pyrrole
25
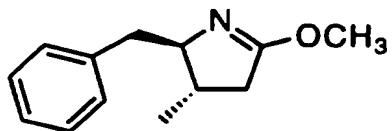
A solution of the product of Example 62 (400 mg, 2.0 mmol)
in methylene chloride (25 mL) was treated with
30 trimethyloxonium tetrafluoroborate (361 mg, 2.4 mmol) by the
method of Example 3 to produce the title material (300 mg,
40%).

Example 64

(±)(*trans*) 4-methyl-5-(phenylmethyl)pyrrolidin-2-imine, monohydrochloride
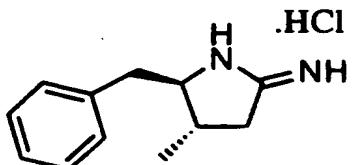
A solution of the title product of Example 63 (300 mg, 1.4 mmol) in MeOH (20 mL) was reacted with ammonium chloride (77 mg, 1.6 mmol) by the method of Example 5 followed by chromatography to generate the title material (240 mg, 75%).

MS (CI) for $C_{12}H_{17}N_2$ (MW = 188): m+ 189 (100 %).
Purity by analytical HPLC 97%.

Example 65

2-(2-propenyl)cycloheptanone
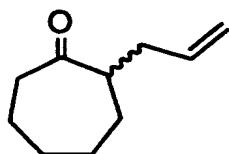
To a mechanically stirred mixture of potassium t-butoxide (Aldrich, 67.0 g, 0.6 mol) in benzene (600 mL) cooled to 0 °C under a nitrogen atmosphere was added cycloheptanone (Aldrich, 56.1 g, 0.5 mol) dropwise over 15 minutes. Ten minutes after the addition was complete, allyl bromide (Aldrich, 61.6 g, 0.51 mol) was added dropwise over 20 minutes. The reaction was warmed to room temperature, refluxed for 7 hrs., stirred at room temperature for 18 hrs., and diluted with 0.5 N KHSO₄ (300 mL). This mixture was further diluted with Et₂O (600 mL), 0.5 N

KHSO4 (200 mL) and H2O (200 mL) before the organic was separated, washed with H2O (200 mL) and brine (200 mL), dried (Na2SO4), filtered, and stripped of all solvent under reduced pressure. The crude product (76.1 g) was distilled to yield 24.4 g (32%) of the title material (bp = 104-108 °C, 25 mm of Hg).

Elemental analysis: $C_{10}H_{16}O$ (MW = 152.24)

	C	H
Calculated:	78.90	10.59
Found:	78.96	10.36

Example 66

2-(2-propenyl)cycloheptanone, oxime
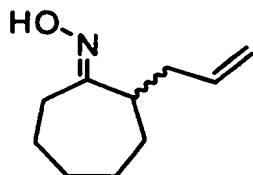
The title material of Example 65 (15.0 g, 98.5 mmol) was converted to the title compound by the method of Example 1 using 10.3 g (98.5 mmol) of hydroxylamine hydrochloride and 14.5 g (180.0 mmol) of NaOAc in a mixture of 90 mL of EtOH and 60 mL of water. The procedure produced 16.4 g (97%) of the title compound.

Elemental analysis: $C_{10}H_{17}NO \cdot 0.25 H_2O$ (MW = 171.75)

	C	H	N
Calculated:	69.93	10.27	8.16
Found:	69.67	10.08	8.03

Example 67

octahydro-8-(2-propenyl)azocin-2-one, mixture with
5   octahydro-3-(2-propenyl)azocin-2-one

Isomer-A   Isomer-B
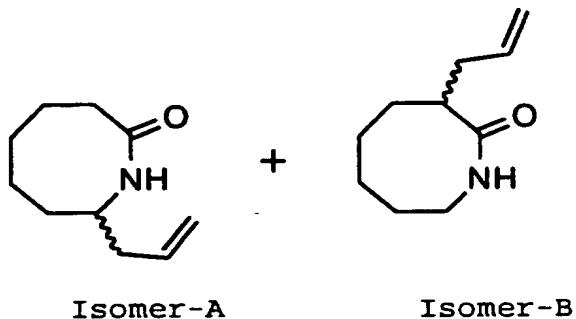
10   To the title product of Example 66 (16.2 g, 96.9 mmol) in
115 mL of acetone containing 1N NaOH (110 mL, 110 mmol)
cooled to 0 °C was added benzenesulfonyl chloride (17.6 g,
100 mmol) dropwise over 10 minutes. The reaction mixture
was warmed to room temperature and stirred over night.
15   After removing the acetone under reduced pressure, the
residue was diluted with EtOAc (300 mL) and water (75 mL).
The aqueous layer (pH = 1) was separated and the organic
layer was washed with 2 x 100 mL of 5% KHCO$_3$ and 2 x 75 mL
of brine, dried over Na$_2$SO$_4$, filtered, and stripped of all
20   solvent under reduced pressure. The crude residue (15.6 g)
was separated into its Isomer-A (5.6 g, 34%) and Isomer-B
(4.8 g, 29%) components by silica gel chromatography.

Isomer-A:
25   Elemental analysis: C$_{10}$H$_{17}$NO · 0.125 H$_2$O (MW = 169.50)

	C	H	N
Calculated:	70.86	10.26	8.26
Found:	70.68	10.22	8.19

30
Isomer-B:
Elemental analysis: C$_{10}$H$_{17}$NO · 0.25 H$_2$O (MW = 171.75)

	C	H	N
Calculated:	69.93	10.27	8.16
Found:	70.15	10.19	8.06

5

Example 68

octahydro-8-(3-phenyl-2-propenyl)azocin-2-one
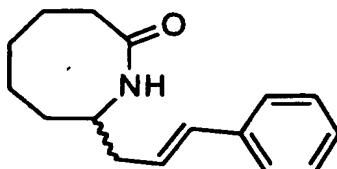
10

The Isomer A of the title material of Example 67 in
acetonitrile is coupled to bromobenzene in the presence
palladium acetate, tri-o-tolylphosphine, and
15   triethylamine by the method of Example 32 to provide the
title material.

Example 69

20

2,3,4,5,6,7-hexahydro-8-methoxy-2-(3-phenyl-2-
propenyl)azocine

25
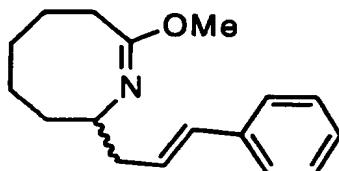
The product of Example 68 is reacted with
trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the
method of Example 3 to produce the title material.

30

Example 70

octahydro-8-(3-phenyl-2-propenyl)azocin-2-imine, monohydrochloride
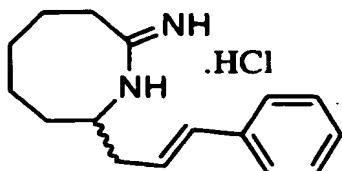
The title product of Example 69 in MeOH is reacted with ammonium chloride by the method of Example 5 to generate the title material.

Example 71

octahydro-8-(3-phenylpropyl)azocin-2-one
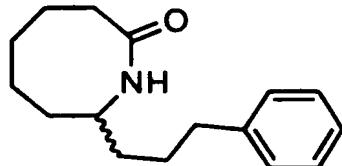
The title material of Example 68 in MeOH is hydrogenated over Pd on carbon in a standard Parr apparatus by the method of Example 35 to generate the title product.

Example 72

2,3,4,5,6,7-hexahydro-8-methoxy-2-(3-phenylpropyl)azocine
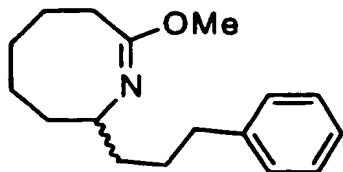
The product of Example 71 is reacted with trimethyloxonium tetrafluoroborate in CH$_2$Cl$_2$ by the method of Example 3 to produce the title material.

Example 73

octahydro-8-(3-phenylpropyl)azocin-2-imine, monohydrochloride
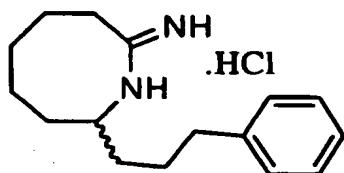
The title product of Example 72 in MeOH is reacted with ammonium chloride by the method of Example 5 to generate the title material.

Example 74

ethyl 1,4-dioxaspiro[4.5]decane-6-carboxylate
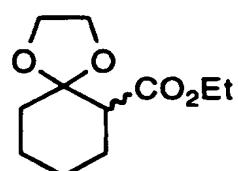
To ethyl 2-cyclohexanonecarboxylate (Aldrich, 169.5 g, 1.0 mol) and ethylene glycol (Sigma, 166.7 g, 2,7 mol) in benzene (1.5 L) was added pyridinium tosylate (50.2 g, 0.2 mol). The reaction was refluxed under a nitrogen atmosphere and the water generated was removed using a Dean-Stark trap. After cooling the reaction to room temperature, half of the benzene was removed under reduced pressure and the residue was washed with 25%

aqueous NaHCO₃, stripped of all solvent, dissolved in
CH₂Cl₂, dried (Na₂SO₄), filtered, and again stripped of
all solvent under reduced pressure to provide 213 g of
the title material.

5

Example 75

1,4-dioxaspiro[4.5]decane-6-carboxaldehyde

10
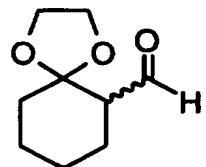
To the product of Example 74 (10.0 g, 46.7 mmol) in 150
mL of toluene cooled to -78 °C was added dropwise under
15   argon (Ar) 93.5 mL (93.5 mmol) of diisobutylaluminum
hydride (DIBAL) in toluene over a 15 min. period. After
stirring this reaction for 45 min., MeOH (40 mL) was
added dropwise followed by 200 mL of a saturated solution
of Rochelle salts (potassium sodium tartrate
20   tetrahydrate). The reaction was warmed to room
temperature, stirred for one hour, and the organic layer
was separated. The aqueous layer was washed with EtOAc
and the organic layer was stripped of all toluene. The
residue and the EtOAc extract were combined, diluted with
25   EtOAc, washed with water, dried (MgSO₄), filtered and
stripped of all solvent to yield the crude desired
product. This material was chromatographed through
silica gel eluting with a 1:1 mixture of EtOAc and hexane
to yield 6.4 g of the title material as a colorless oil.

30

Example 76

2-ethenylcyclohexanone
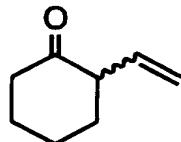
5

To a cold suspension of methylphosphonium bromide in Et$_2$O under Ar is added an Et$_2$O solution of potassium hexamethyldisilylazide (KHMDS). After stirring this
10   mixture for one hr, the title material of Example 75, dissolved in Et$_2$O, is added dropwise to the stirred reaction mixture. The reaction is allowed to stir cold, warm to room temperature and to stir at room temperature. After quenching the reaction with water, it is extracted
15   with Et$_2$O, dried, stripped of solvent under reduced pressure to yield the crude product. The title material is isolated from the crude product by silica gel chromatography. Alternatively, the title material is synthesized by the method described by S. Kim and S. Lee,
20   *Tetrahedron Letters*, **1991**, 32, 6575-6578.

Example 77

25   2-ethenylcyclohexanone, oxime
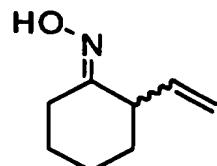
The product of Example 76 is reacted with hydroxylamine
30   hydrochloride and NaOAc in a mixture of EtOH and water, by the method of Example 1 to produce the title material.

Example 78

7-ethenylhexahydro-2H-azepin-2-one, mixture with 3-
ethenylhexahydro-2H-azepin-2-one

5
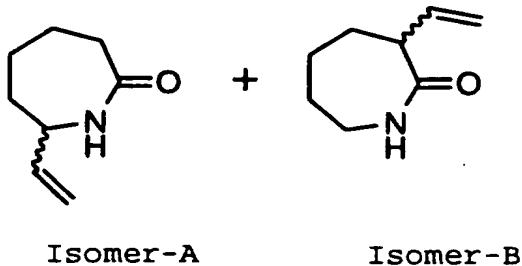
Isomer-A   Isomer-B

The title product of Example 77 in acetone containing 1N
10   NaOH is reacted with benzenesulfonyl chloride by the method
described in Example 67 to generate the Isomer-A and Isomer-
B title materials.

15   Example 79

methyl 2-[2-(hexahydro-7-oxo-1H-azepin-2-
yl)ethenyl]benzoate

20
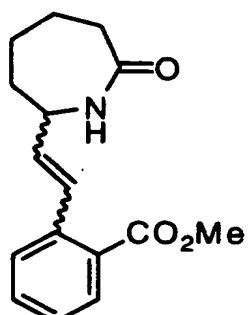
The Isomer A of the title material of Example 78 in
acetonitrile is coupled to methyl 2-bromobenzoate
(Aldrich) in the presence palladium acetate, tri-o-
25   tolylphosphine, and triethylamine by the method of
Example 32 to provide the title material as either or
both the Z and E isomers.

Example 80

methyl 2-[2-(3,4,5,6-tetrahydro-7-methoxy-2H-azepin-2-yl)ethenyl]benzoate

5
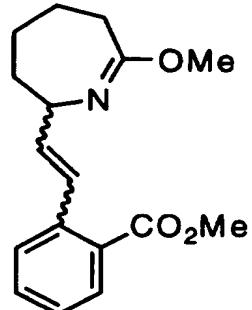
The product of Example 79 is reacted with trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the
10   method of Example 3 to produce the title material.

Example 81

15   methyl 2-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethenyl]benzoate, monohydrochloride
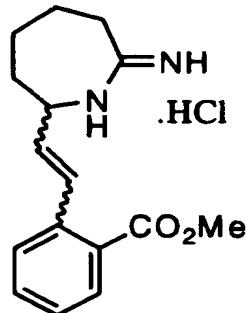
20   The title product of Example 80 in MeOH is reacted with ammonium chloride by the method of Example 5 to generate the title material.

Example 82

methyl 2-[2-(hexahydro-7-oxo-1H-azepin-2-yl)ethyl]benzoate

5
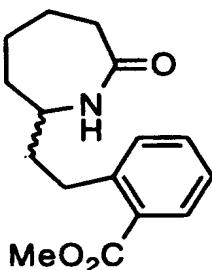
The title material of Example 79 in MeOH is hydrogenated over Pd on carbon in a standard Parr apparatus by the method of Example 35 to generate the title product.

10

Example 83

15   methyl 2-[2-(3,4,5,6-tetrahydro-7-methoxy-2H-azepin-2-yl)ethyl]benzoate
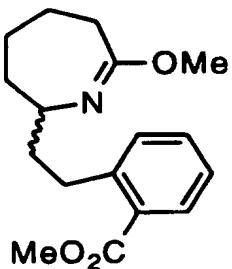
20   The product of Example 82 is reacted with trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the method of Example 3 to produce the title material.

Example 84

methyl 2-[2-(hexahydro-7-imino-1H-azepin-2-
yl)ethyl]benzoate, monohydrochloride
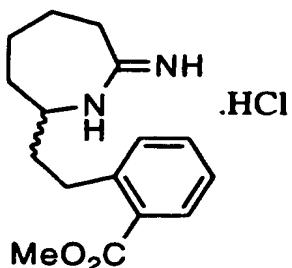
The title product of Example 83 in MeOH is reacted with
ammonium chloride by the method of Example 5 to generate the
title material.

Example 85

methyl 2-[2-(hexahydro-2-oxo-1H-azepin-3-
yl)ethenyl]benzoate

The Isomer B of the title material of Example 78 in
acetonitrile is coupled to methyl 2-bromobenzoate
(Aldrich) in the presence palladium acetate, tri-o-
tolylphosphine, and triethylamine by the method of
Example 32 to provide the title material as either or
both the Z and E isomers.

Example 86

5   methyl 2-[2-(3,4,5,6-tetrahydro-7-methoxy-2H-azepin-6-yl)ethenyl]benzoate
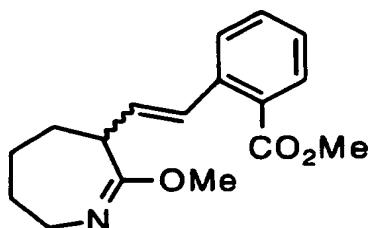
The product of Example 85 is reacted with
10   trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the method of Example 3 to produce the title material.

Example 87

15

methyl 2-[2-(hexahydro-2-imino-1H-azepin-3-yl)ethenyl]benzoate, monohydrochloride

20
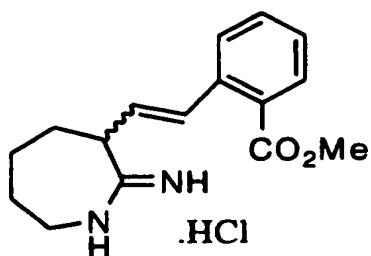
The title product of Example 86 in MeOH is reacted with ammonium chloride by the method of Example 5 to generate the title material.

Example 88

methyl 2-[2-(hexahydro-2-oxo-1H-azepin-3-yl)ethyl]benzoate
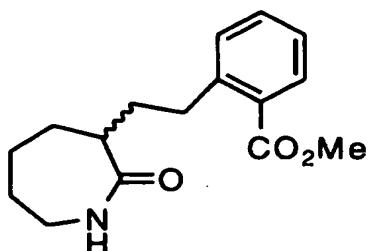
The title material of Example 85 in MeOH is hydrogenated over Pd on carbon in a standard Parr apparatus by the method of Example 35 to generate the title product.

Example 89

methyl 2-[2-(3,4,5,6-tetrahydro-7-methoxy-2H-azepin-6-yl)ethyl]benzoate
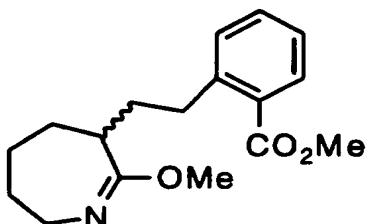
The product of Example 88 is reacted with trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the method of Example 3 to produce the title material.

Example 90

methyl 2-[2-(hexahydro-2-imino-1H-azepin-3-
yl)ethyl]benzoate, monohydrochloride

5
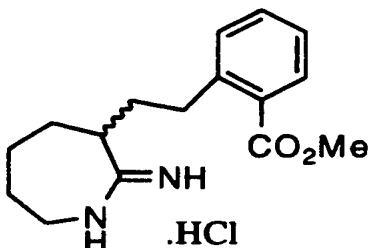
The title product of Example 89 in MeOH is reacted with
ammonium chloride by the method of Example 5 to generate the
10   title material.

Example 91

15   methyl 3-[2-(hexahydro-7-oxo-1H-azepin-2-yl)ethenyl]
benzeneacetate
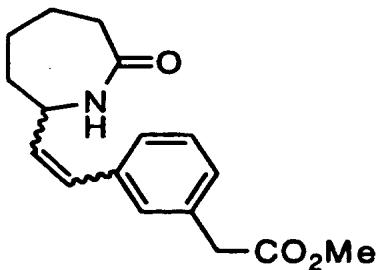
20   The Isomer A of the title material of Example 78 in
acetonitrile is coupled to methyl 3-bromobenzeneacetate
(Aldrich) in the presence palladium acetate, tri-o-
tolylphosphine, and triethylamine by the method of
Example 32 to provide the title material as either or
25   both the Z and E isomers.

Example 92

methyl 2-[2-(3,4,5,6-tetrahydro-7-methoxy-2H-azepin-6-yl)ethenyl] benzeneacetate

5
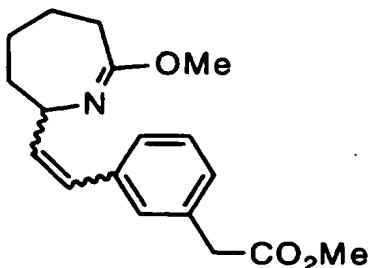
The product of Example 91 is reacted with trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the
10   method of Example 3 to produce the title material.

Example 93

15   methyl 3-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethenyl] benzeneacetate, monohydrochloride
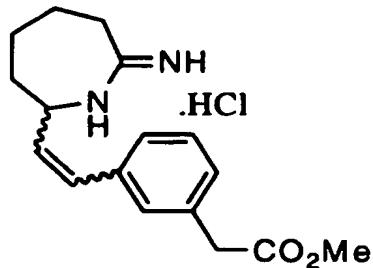
20   The title product of Example 92 in MeOH is reacted with ammonium chloride by the method of Example 5 to generate the title material.

Example 94

6-(phenylmethyl)piperidin-2-imine, monohydrochloride
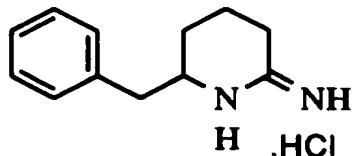
2-benzylpyridine (Aldrich, 2.5 g, 0.015 mole), sodium
amide (780 mg, 0.02 mole) and N, N-dimethylaniline (25
mL) were refluxed overnight. Contents were allowed to
cool and partitioned between ether (Et_2O) and water. The
ether layer was dried ($MgSO_4$) and concentrated in vacuo
leaving an oil. The oil was purified by chromatography.
The purified material was dissolved in 1N HCl,
lyophilized, and triturated with EtOAc to give 2-amino-6-
benzylpyridine as a white solid. This 2-amino-6-
benzylpyridine (470 mg), 5% rhodium/carbon (250 mg), and
glacial acetic acid (30 mL) were shaken at 55 psi
hydrogen on a Parr hydrogenation apparatus overnight.
More catalyst (300 mg) was added and contents were again
shaken at 55 psi hydrogen overnight. Contents were
filtered and the filtrate was concentrated in vacuo
leaving a viscous oil (500 mg). The product was purified
by C-18 reverse phase chromatography to give a white
solid. The solid was dissolved in 1 N HCl, lyophilized,
and recrystallized from EtOH/EtOAc to give the desired as
a white solid. The analysis of the product was found to
be consistent with the proposed structure.

MH+ = 189.
^{1}H NMR ($CDCl_3$):   d 9.85 (s, 1H); 8.95 (s, 1H); 8.62 (s,
1H); 7.40 - 7.10 (m, 5H); 3.80 - 3.60 (m, 1H); 3.20 -
3.00 (m, 1H); 2.90 - 2.70 (m, 2H); 2.65 - 2.45 (m, 1H);
2.42 - 2.25 (m, 2H); 1.92 (m, 2H); 1.75 (m, 1H); 1.50 -
1.35 (m, 1H).

Example 95

6-(cyclohexylmethyl)piperidin-2-imine, monohydrochloride
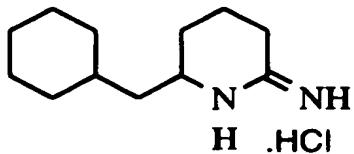
5

The 2-amino-6-benzylpyridine was reduced as in Example
94, except platinum oxide was used as the catalyst. The
product was obtained as an oil which was dissolved in 1 N
10 HCl and lyophilized to give a white solid. The solid was
recrystallized from EtOAc to give the desired title
compound as white crystals. The analysis of the product
was found to be consistent with the proposed structure.

15 MH+ = 195.
1H NMR (CDC13):   d 9.60 (s, 1H); 8.90 (s, 1H); 8.70 (s,
1H); 3.60 - 3.40 (m, 1H); 2.90 - 2.70 (m, 1H); 2.70 -
2.50 (m, 1H); 2.10 - 1.80 (m, 2H); 1.80 - 1.00 (m, 13H);
1.00 - 0.80 (m, 2H).
20

Example 96

6-(3-phenyl-2-propenyl)piperidin-2-one
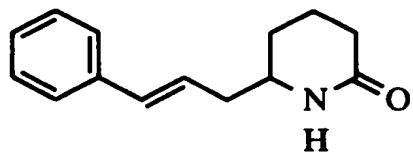
25

6-Allyl valerolactam is reacted with bromobenzene by the
method of Example 32 to generate the title compound.

Example 97

2,3,4,5-tetrahydro-6-methoxy-2-(3-phenyl-2-
propenyl)pyridine

5
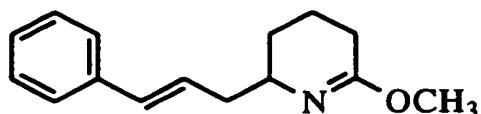
The product of Example 96 is reacted with
trimethyloxonium tetrafluoroborate by the method of
10   Example 3 to generate the title compound.

Example 98

15   6-(3-phenyl-2-propenyl)piperidin-2-imine,
monohydrochloride
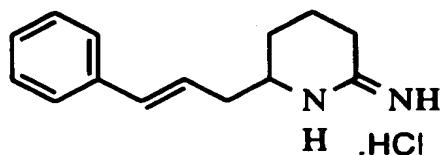
20   The product of Example 97 is reacted with ammonium
chloride by the method of Example 5 to generate the title
compound.

25   Example 99

6-(3-phenylpropyl)piperidin-2-one
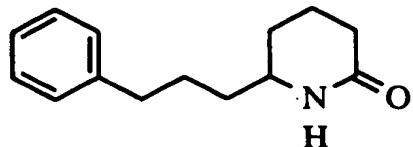
30

The product of Example 96 is hydrogenated by the method of Example 35 to generate the title compound.

Example 100

2,3,4,5-tetrahydro-6-methoxy-2-(3-phenylpropyl)pyridine
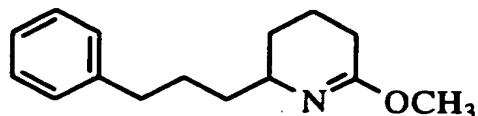
The product of Example 99 is reacted with trimethyloxonium tetrafluoroborate by the method of Example 3 to generate the title compound.

Example 101

6-(3-phenylpropyl)piperidin-2-imine, monohydrochloride
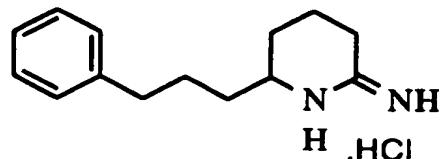
The product of Example 100 is reacted with ammonium chloride by the method of Example 5 to generate the title compound.

Example 102

methyl 1-[2-(1,3-dioxolan-2-yl)ethyl]-2-
oxocyclohexanecarboxylate

5
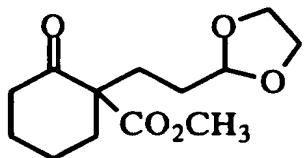
A solution of 2-carbomethoxycyclohexanone (2.0 g, 12.8
mmoles) in 50 mL of DMF was reacted at 70 °C for 15 h
10   with 2-(2-bromoethyl)-1,3-dioxolane (4.6 g, 25 mmoles)
and potassium carbonate (4.8 g, 34.8 mmoles). The
reaction mixture was diluted to 500 mL with water and
extracted with ethyl ether/ethyl acetate. the organic
extracts were dried over sodium sulfate, and the solvent
15   was evaporated to generate the title compound as an oil.
FAB-MS: m/z263 (M+Li).

Example 103

20

2-[2-(1,3-dioxolan-2-yl)ethyl]cyclohexanone
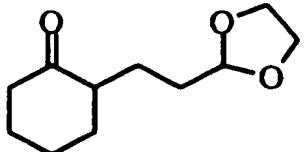
25   The product of Example 102 was reacted with sodium
cyanide (0.69 g, 14.1 mmoles) in 25 mL of DMSO at 160 °C
for 12 hrs. The reaction mixture was then diluted to 700
mL with water and extracted with ethyl acetate/hexane
(1:1). The solvent removed from the extracts to provide
30   the title compound as oil.
FAB-MS: m/z205.7 (M+Li).

Example 104

2-[2-(1,3-dioxolan-2-yl)ethyl]cyclohexanone, oxime
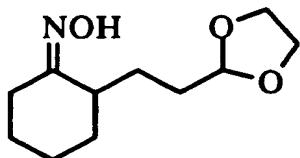
The product of Example 103 was reacted with hydroxylamine hydrochloride (1.25 g, 18 mmoles) and sodium acetatetrihydrate (2.9 g, 21 mmoles) in 30 mL ethanol/water (2:1) for 4 hrs under gentle reflux. The solvent was evaporated and the solid dissolved in ethyl acetate, washed with sat. sodium chloride, dried over sodium sulfate, and the solvent stripped off to leave the title compound as an oil.

FAB-MS: m/z214.1 (M+H).

Example 105

7-[2-(1,3-dioxolan-2-yl)ethyl]hexahydro-2H-azepin-2-one
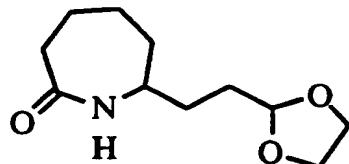
The product of Example 104 is reacted with benzenesulfonyl chloride and sodium hydroxide in acetone/water by the method of Example 67 to generate the title compound.

Example 106

2-[2-(1,3-dioxolan-2-yl)ethyl]-3,4,5,6-tetrahydro-7-methoxy-2H-azepine

5
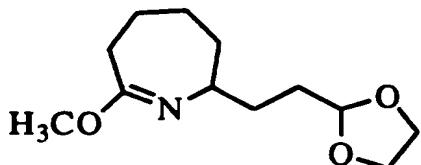
The product of Example 105 is reacted with
trimethyloxonium tetrafluoroborate by the method of
10   Example 3 to generate the title compound.

Example 107

15   7-[2-(1,3-dioxolan-2-yl)ethyl]hexahydro-2H-azepin-2-
imine, monohydrochloride
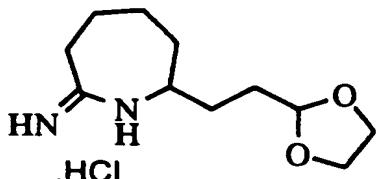
20   The product of Example 106 is reacted with ammonium
chloride by the method of Example 5 to generate the title
compound.

Example 108

methyl 1-[2-(1,3-dioxan-2-yl)ethyl]-2-
oxocyclohexanecarboxylate
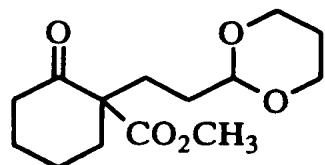
A solution of 2-carbomethoxycyclohexanone in DMF is
reacted with 2-(2-bromoethyl)-1,3-dioxane and potassium
carbonate by the method of Example 102 to generate the
title compound.

Example 109

2-[2-(1,3-dioxan-2-yl)ethyl]cyclohexanone
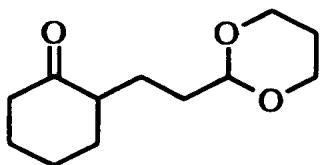
The product of Example 108 is reacted with sodium cyanide
in DMSO at 160 °C by the method of Example 103 to
generate the title compound.

Example 110

2-[2-(1,3-dioxan-2-yl)ethyl]cyclohexanone, oxime
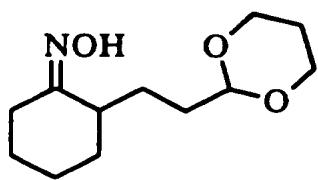
The product of Example 109 is reacted with hydroxylamine
hydrochloride and sodium acetate in ethanol/water by the
method of Example 1 to generate the title compound.

5

Example 111

7-[2-(1,3-dioxan-2-yl)ethyl]hexahydro-2H-azepin-2-one

10
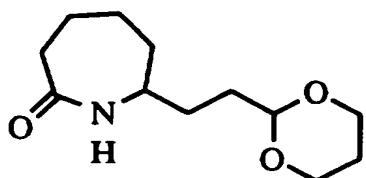
The product of Example 110 is reacted with
benzenesulfonyl chloride and sodium hydroxide in

15   acetone/water by the method of Example 67 to generate the
title compound.

Example 112

20   2-[2-(1,3-dioxan-2-yl)ethyl]-3,4,5,6-tetrahydro-7-
methoxy-2H-azepine
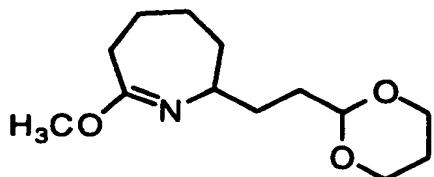
25   The product of Example 111 is reacted with
trimethyloxonium tetrafluoroborate by the method of
Example 3 to generate the title compound.

Example 113

7-[2-(1,3-dioxan-2-yl)ethyl]hexahydro-2H-azepin-2-imine,
monohydrochloride

5
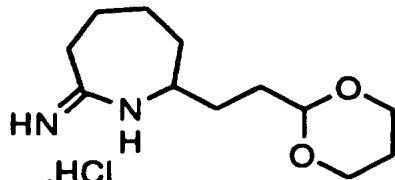
The product of Example 112 is reacted with ammonium
chloride by the method of Example 5 to generate the title
10   compound.

Example 114

15   7-[[4,5-dihydro-3-(trifluoromethyl)isoxazol-5-
yl]methyl]hexahydro-2H-azepin-2-one, mixture with 7-
[[4,5-dihydro-3-(trifluoromethyl)isoxazol-4-
yl]methyl]hexahydro-2H-azepin-2-one
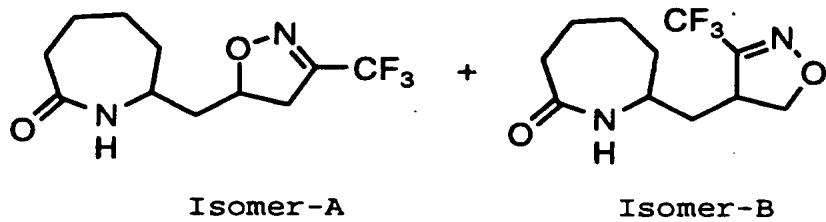
Isomer-A   Isomer-B

20

The title product isomer B of Example 18 (7-allyl
caprolactam) is reacted with trifluoromethyloximoyl
25   chloride and triethylamine in toluene by the method of R.
Huisgen, *Ang. Chem. Int. Ed.* **1963**, 2(10), 562, to
generate a mixture of the two title compounds. The title
Isomer-A and Isomer-B materials are separated by HPLC.

Example 115

2-[[4,5-dihydro-3-(trifluoromethyl)isoxazol-5-yl]methyl]-
3,4,5,6-tetrahydro-7-methoxy-2H-azepine
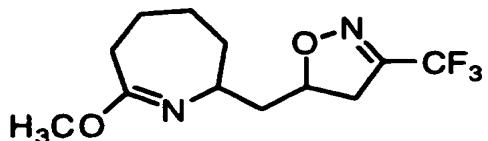
5

The title Isomer-A of Example 114 is reacted with
trimethyloxonium tetrafluoroborate by the method of
10   Example 3 to generate the title compound.

Example 116

15   7-[[4,5-dihydro-3-(trifluoromethyl)isoxazol-5-
yl]methyl]hexahydro-2H-azepin-2-imine, monohydrochloride
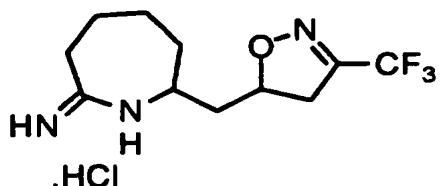
20   The product of Example 115 is reacted with ammonium
chloride by the method of Example 5 to generate the title
compound.

Example 117

2-[[4,5-dihydro-3-(trifluoromethyl)isoxazol-4-yl]methyl]-
3,4,5,6-tetrahydro-7-methoxy-2H-azepine
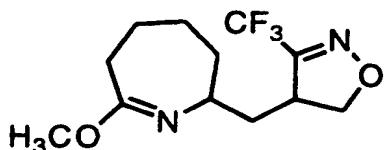
5

The title Isomer-B of Example 114 is reacted with
trimethyloxonium tetrafluoroborate by the method of
10   Example 3 to generate the title compound.

Example 118

7-[[4,5-dihydro-3-(trifluoromethyl)isoxazol-4-
15   yl]methyl]hexahydro-2H-azepin-2-imine, monohydrochloride
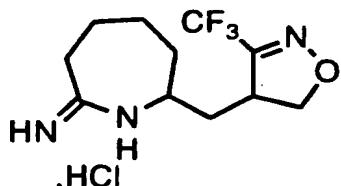
The title product of Example 117 is reacted with ammonium
20   chloride by the method of Example 5 to generate the title
compound.

Example 119

25

hexahydro-7-[[3-(trifluoromethyl)isoxazol-5-yl]methyl]-
2H-azepin-2-one
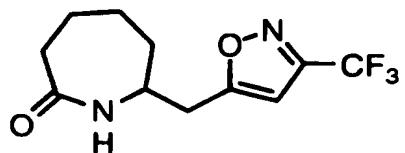
The title Isomer-A of Example 114 is reacted with
manganese dioxide in benzene/dioxane by the method of A.
Barco, *Synth. Commun.* **1978**, 8, 219, to generate the
5   title compound.

Example 120

10   3,4,5,6-tetrahydro-7-methoxy-2-[[3-
(trifluoromethyl)isoxazol-5-yl]methyl]-2H-azepine
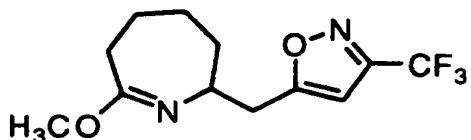
15   The title product of Example 119 is reacted with
trimethyloxonium tetrafluoroborate by the method of
Example 3 to generate the title compound.

Example 121

20

hexahydro-7-[[3-(trifluoromethyl)isoxazol-5-yl]methyl]-
2H-azepin-2-imine, monohydrochloride
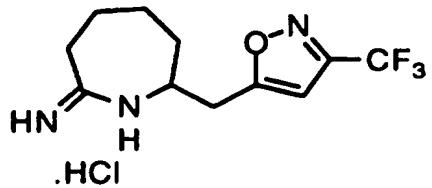
25

The title product of Example 120 is reacted with ammonium
chloride by the method of Example 5 to generate the title
compound.

Example 122

hexahydro-7-[[3-(trifluoromethyl)isoxazol-4-yl]methyl]-
2H-azepin-2-one
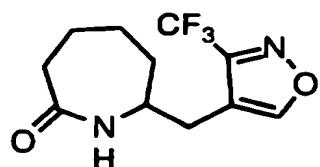
5

The title Isomer-B of Example 114 is reacted with
manganese dioxide in benzene/dioxane by the method of A.
10 Barco, *Synth. Commun.* **1978**, 8, 219 , to generate the
title compound.

Example 123

15

3,4,5,6-tetrahydro-7-methoxy-2-[[3-
(trifluoromethyl)isoxazol-4-yl]methyl]-2H-azepine

20
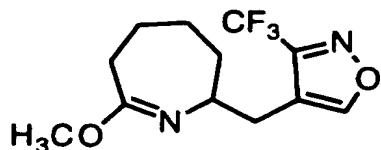
The title product of Example 122 is reacted with
trimethyloxonium tetrafluoroborate by the method of
Example 3 to generate the title compound.

Example 124

hexahydro-7-[[3-(trifluoromethyl)isoxazol-4-yl]methyl]-
2H-azepin-2-imine, monohydrochloride

5
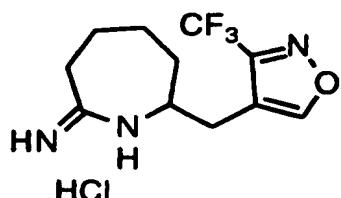
The title product of Example 123 is reacted with ammonium
chloride by the method of Example 5 to generate the title
10   compound.

Example 125

15   7-[(4,5-dihydro-3-phenylisoxazol-4-yl)methyl]hexahydro-
2H-azepin-2-one, mixture with 7-[(4,5-dihydro-3-
phenylisoxazol-5-yl)methyl]hexahydro-2H-azepin-2-one

20   Isomer-A   Isomer-B
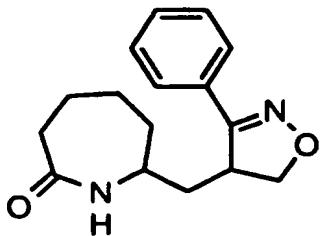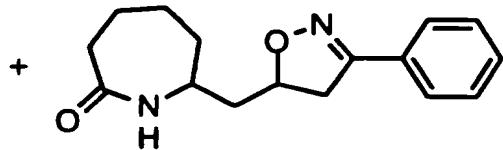
The title product Isomer B of Example 18 (7-Allyl
caprolactam) is reacted with benzaldehydeoximinoyl
chloride and triethylamine in toluene by the method of R.
25   Huisgen, *Ang. Chem. Int. Ed.* **1963**, 2(10), 562: To a
solution of 2 g (0.013 mol) of benzaldehyde oximinoyl
chloride and 1g (0.006 mol) of 7-allylcaprolactam in 30mL
of ethyl ether was added 1.3 g (0.013 mol) of
triethylamine dropwise. This mixture was stirred at 25
30   °C for 18 hours. The mixture was then diluted with ethyl

acetate, washed with dilute HCl, dried (MgSO4), filtered
and concentrated to afford an off-white semi-solid.
Trituration with ethyl ether and filtration afforded 1.1
g of an off-white solid. Column chromatography (ethyl
5   acetate) afforded a mixture of the title compounds as a
white solid, mp = 118-128°C, M+H = 273. The title
Isomer-A and Isomer-B materials are separated by HPLC.

Example 126

10

hexahydro-7-[(3-phenylisoxazol-4-yl)methyl]-2H-azepin-2-
one
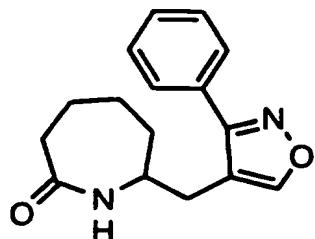
15

The title Isomer-A material of Example 125 is reacted
with manganese dioxide in benzene/dioxane by the method
of A. Barco, *Synth. Commun.* **1978**, 8, 219, to generate
the title compound.

20

Example 127

3,4,5,6-tetrahydro-7-methoxy-2-[(3-phenylisoxazol-4-
25   yl)methyl]-2H-azepine
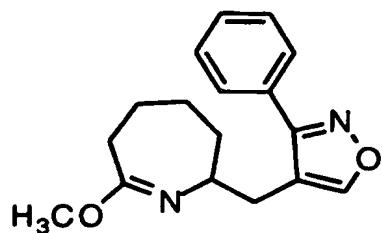
The title product of Example 126 is reacted with
trimethyloxonium tetrafluoroborate by the method of
Example 3 to generate the title compound.

5

Example 128

hexahydro-7-[(3-phenylisoxazol-4-yl)methyl]-2H-azepin-2-
imine, monohydrochloride

10
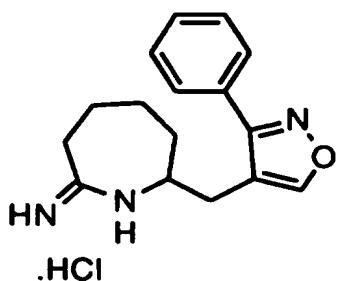
The title product of Example 127 is reacted with ammonium
chloride by the method of Example 5 to generate the title
15   compound.

Example 129

20   hexahydro-7-[(3-phenylisoxazol-5-yl)methyl]-2H-azepin-2-
one
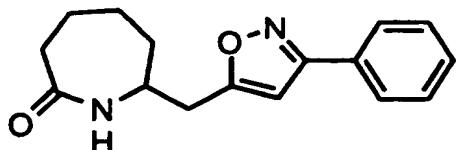
25   The title Isomer-B material of Example 125 is reacted
with manganese dioxide in benzene/dioxane by the method
of A. Barco, *Synth. Commun.* **1978**, 8, 219 , to generate
the title compound.

Example 130

3,4,5,6-tetrahydro-7-methoxy-2-[(3-phenylisoxazol-5-
yl)methyl]-2H-azepine

5
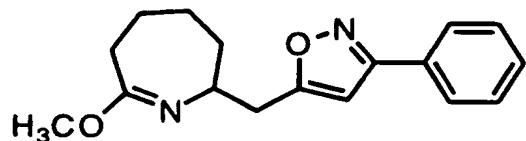
The product of Example 129 is reacted with
trimethyloxonium tetrafluoroborate by the method of
10   Example 3 to generate the title compound.

Example 131

15   hexahydro-7-[(3-phenylisoxazol-5-yl)methyl]-2H-azepin-2-
imine, monohydrochloride
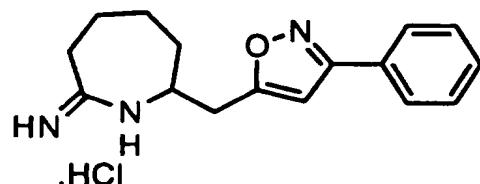
20   The product of Example 130 is reacted with ammonium
chloride by the method of example 5 to generate the title
compound.

Example 132

7-[[4,5-dihydro-1-phenyl-3-(trifluoromethyl)-2H-pyrazol-
5-yl]methyl]hexahydro-1H-azepin-2-one, mixture with 7-
5   [[4,5-dihydro-1-phenyl-3-(trifluoromethyl)-2H-pyrazol-4-
yl]methyl]hexahydro-1H-azepin-2-one
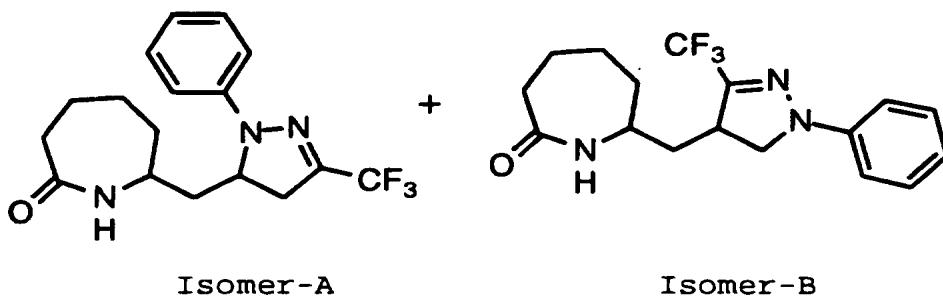
Isomer-A   Isomer-B

10

The title product Isomer B of Example 18 (7-Allyl
caprolactam) is reacted with
trifluoroacetaldehydebenzenehydrazonoyl chloride and
triethylamine in toluene by the method of R. Huisgen,
15   *Ang. Chem. Int. Ed.* **1963**, 2(10), 562,   to generate a
mixture of the two title compounds. The title Isomer-A
and Isomer-B materials are separated by HPLC.

20   Example 133

2-[[4,5-dihydro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-
5-yl]methyl]-3,4,5,6-tetrahydro-7-methoxy-2H-azepine

25
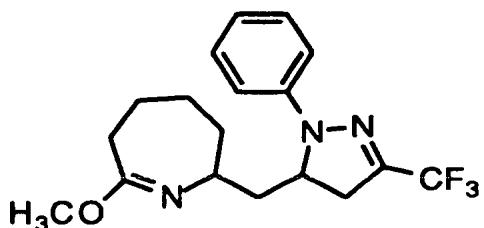
The title Isomer-A material of Example 132 is reacted
with trimethyloxonium tetrafluoroborate by the method of
Example 3 to generate the title compound.

Example 134

7-[[4,5-dihydro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-
5-yl]methyl]-hexahydro-2H-azepin-2-imine,
monohydrochloride
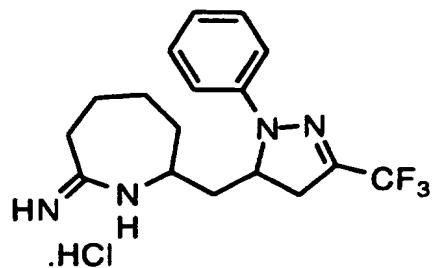
The title product of Example 133 is reacted with ammonium
chloride by the method of Example 5 to generate the title
compound.

Example 135

2-[[4,5-dihydro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-
4-yl]methyl]-3,4,5,6-tetrahydro-7-methoxy-2H-azepine
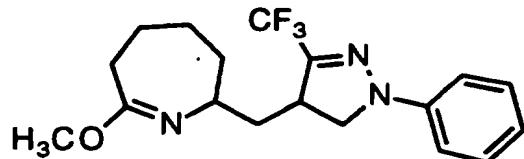
The title Isomer-B material of Example 132 is reacted
with trimethyloxonium tetrafluoroborate by the method of
Example 3 to generate the title compound.

Example 136

7-[[4,5-dihydro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-
4-yl]methyl]hexahydro-2H-azepin-2-imine,
5   monohydrochloride
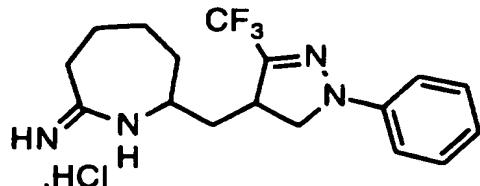
The title product of Example 135 is reacted with ammonium
10   chloride by the method of Example 5 to generate the title
compound.

Example 137
15

hexahydro-7-[[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-
yl]methyl]-2H-azepin-2-one
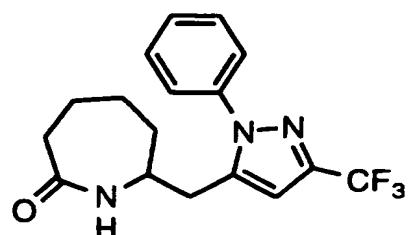
20

The title Isomer-A material of Example 132 is reacted
with DDQ in benzene by the method of E. W. Bousquet, *J.
Org. Chem.* **1975**, 40, 2208, to generate the title
compound.

25

Example 138

3,4,5,6-tetrahydro-7-methoxy-2-[[1-phenyl-3-
(trifluoromethyl)-1H-pyrazol-5-yl]methyl]-2H-azepine

5
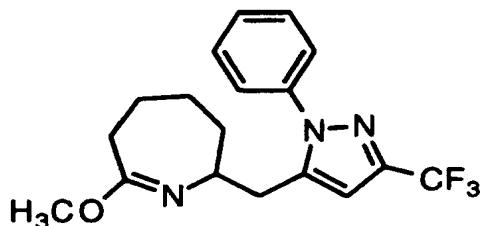
The title material of Example 137 is reacted with
trimethyloxonium tetrafluoroborate by the method of
10   Example 3 to generate the title compound.

Example 139

15   hexahydro-7-[[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-
yl]methyl]-2H-azepin-2-imine, monohydrochloride
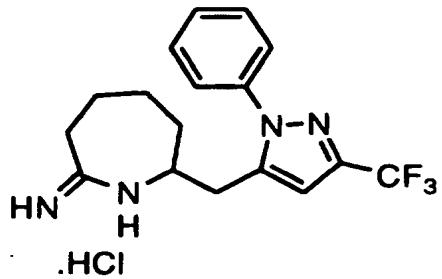
20   The title material of Example 138 is reacted with
ammonium chloride by the method of Example 5 to generate
the title compound.

Example 140

hexahydro-7-[[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl]-2H-azepin-2-one
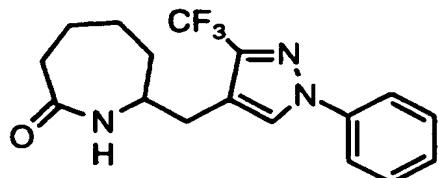
5

The title Isomer-B material of Example 132 is reacted with DDQ in benzene by the method of E. W. Bousquet, *J. Org. Chem.* **1975**, 40, 2208, to generate the title compound.

Example 141

15

3,4,5,6-tetrahydro-7-methoxy-2-[[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl]-2H-azepine

20
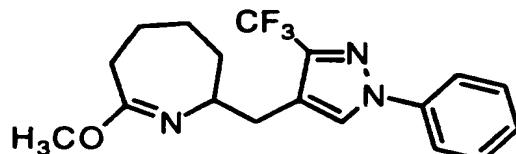
The title material of Example 140 is reacted with trimethyloxonium tetrafluoroborate by the method of Example 3 to generate the title compound.

Example 142

hexahydro-7-[[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-
yl]methyl]-2H-azepin-2-imine, monohydrochloride
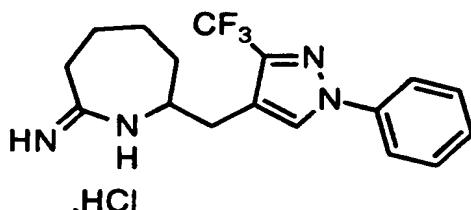
The title material of Example 141 is reacted with
ammonium chloride by the method of Example 5 to generate
the title compound.

Example 143

7-[(4,5-dihydro-1,3-diphenyl-1H-pyrazol-4-
yl)methyl]hexahydro-2H-azepin-2-one, mixture with 7-
[(4,5-dihydro-1,3-diphenyl-1H-pyrazol-5-
yl)methyl]hexahydro-2H-azepin-2-one
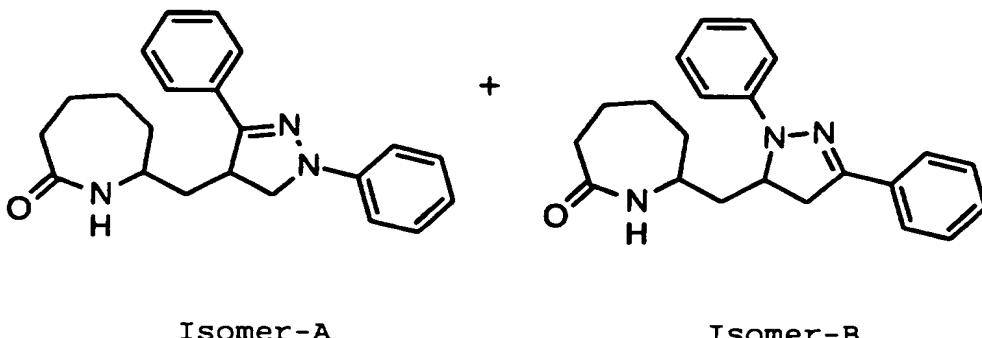
Isomer-A   Isomer-B

The title product Isomer B of Example 18 (7-Allyl
caprolactam) is reacted with benzaldehyde,
benzenehydrazonoyl chloride, and triethylamine in toluene
by the method of R. Huisgen, *Ang. Chem. Int. Ed.* **1963**,
2(10), 562, to generate a mixture of the two title
compounds. The title Isomer-A and Isomer-B materials are
separated by HPLC.

Example 144

2-[(4,5-dihydro-1,3-diphenyl-1H-pyrazol-4-yl)methyl]3,4,5,6-tetrahydro-7-methoxy-2H-azepine

5
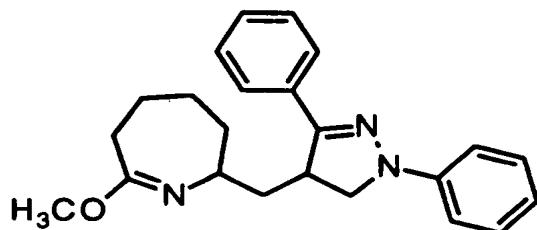
The title Isomer-A material of Example 143 is reacted with trimethyloxonium tetrafluoroborate by the method of Example 3 to generate the title compound.

Example 145

7-[(4,5-dihydro-1,3-diphenyl-1H-pyrazol-4-yl)methyl]hexahydro-2H-azepin-2-imine, monohydrochloride
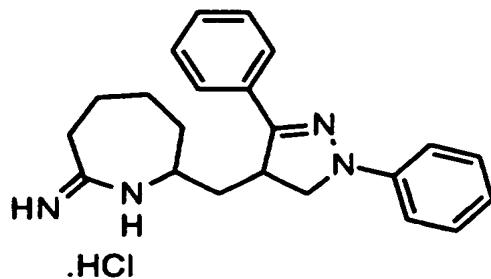

The title material of Example 144 is reacted with ammonium chloride by the method of Example 5 to generate the title compound.

Example 146

7-[(1,3-diphenyl-1H-pyrazol-5-yl)methyl]hexahydro-2H-azepin-2-one

5
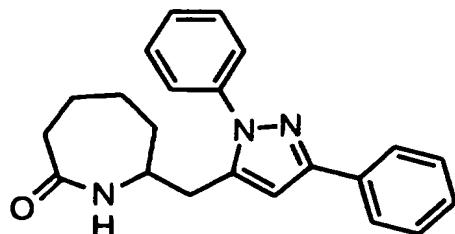
The title Isomer-B material of Example 143 is reacted with DDQ in benzene by the method of E. W. Bousquet, *J.*
10 *Org. Chem.* **1975**, 40, 2208, to generate the title compound.

Example 147

15

2-[(1,3-diphenyl-1H-pyrazol-5-yl)methyl]-3,4,5,6-tetrahydro-7-methoxy-2H-azepine
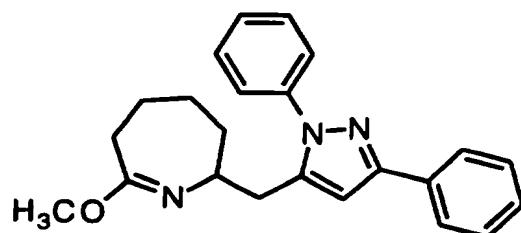
20 The title product of Example 146 is reacted with trimethyloxonium tetrafluoroborate by the method of Example 3 to generate the title compound.

Example 148

7-[(1,3-diphenyl-1H-pyrazol-5-yl)methyl]hexahydro-2H-
azepin-2-imine, monohydrochloride

5

.HCl
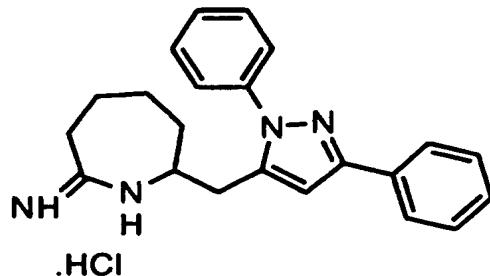
The title material of Example 147 is reacted with
ammonium chloride by the method of Example 5 to generate
10   the title compound.

Example 149

15   2-oxocyclohexaneacetonitrile
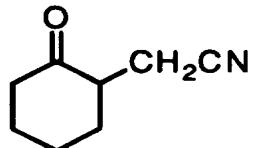
Cyclohexanone is reacted with bromoacetonitrile by the
20   method of Example 65 to generate the title compound.

Example 150

2-(hydroxyimino)cyclohexaneacetonitrile
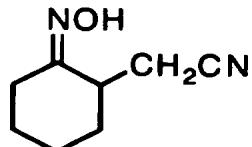
The product of Example 149 is reacted with hydroxylamine hydrochloride and sodium acetate in ethanol/water by the method of Example 1 to generate the title compound.

Example 151

hexahydro-7-oxo-1H-azepine-2-acetonitrile
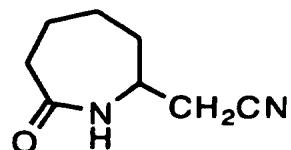
The product of Example 150 is reacted with benzenesulfonyl chloride and sodium hydroxide in acetone/water by the method of Example 67 to generate the title compound.

Example 152

5

hexahydro-7-[[1-phenyl-3-(trifluoromethyl)-1H-1,2,4-
triazol-5-yl]methyl]-2H-azepin-2-one
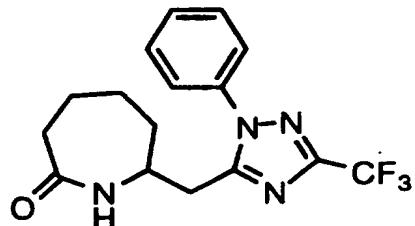
The product of Example 151 is reacted with
trifluoroacetaldehyde, benzenehydrazonoyl chloride, and
10   triethylamine in toluene by the method of R. Huisgen,
Ang. Chem. Int. Ed. **1963**, 2(10), 562, to generate the
title compound.

15   Example 153

3,4,5,6-tetrahydro-7-methoxy-2-[[1-phenyl-3-
(trifluoromethyl)-1H-1,2,4-triazol-5-yl]methyl]-2H-
azepine

20
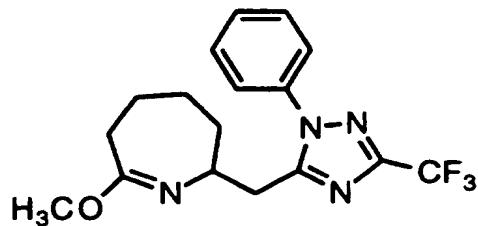


The product of Example 152 is reacted with
trimethyloxonium tetrafluoroborate by the method of
25   Example 3 to generate the title compound.

Example 154

hexahydro-7-[[1-phenyl-3-(trifluoromethyl)-1H-1,2,4-
triazol-5-yl]methyl]-2H-azepin-2-imine, monohydrochloride
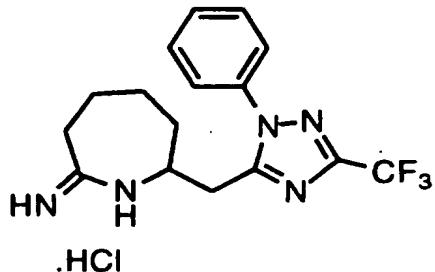

The product of Example 153 is reacted with ammonium
chloride by the method of Example 5 to generate the title
compound.

Example 155

hexahydro-7-[2-(2-nitrophenyl)ethenyl]-2H-azepin-2-one
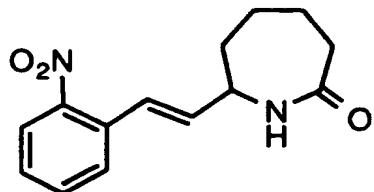
The Isomer A title material of Example 78 in acetonitrile
is coupled to 1-bromo-2-nitrobenzene (Aldrich) in the
presence palladium acetate, tri-o-tolylphosphine, and
triethylamine by the method of Example 32 to provide the
title material as either or both the Z and E isomers.

Example 156

3,4,5,6-tetrahydro-7-methoxy-2-[2-(2-
nitrophenyl)ethenyl]-2H-azepine

5
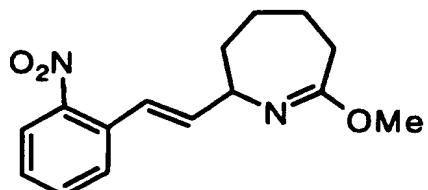
The product of Example 155 is reacted with
trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the

10   method of Example 3 to produce the title material.

Example 157

15   hexahydro-7-[2-(2-nitrophenyl)ethenyl]-2H-azepin-2-imine,
monohydrochloride
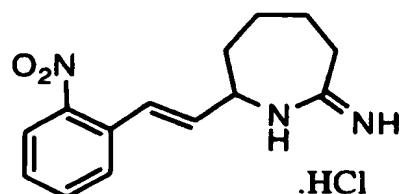
20   The product of Example 156 is reacted with ammonium
chloride by the method of Example 5 to generate the title
compound.

Example 158

2-[2-(hexahydro-7-imino-2H-azepin-2-yl)ethyl]benzenamine, dihydrochloride

5
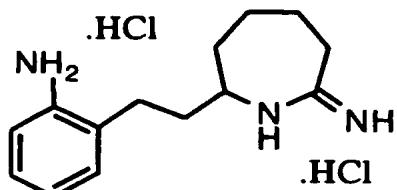
The title material of Example 157 in MeOH is hydrogenated over Pd on carbon in a standard Parr apparatus by the

10   method of Example 35 reducing both the nitro and double bond functions to generate the title product.

Example 159

15

methyl 2-[3-(hexahydro-7-oxo-1H-azepin-2-yl)-1-propenyl]-5-nitrobenzoate
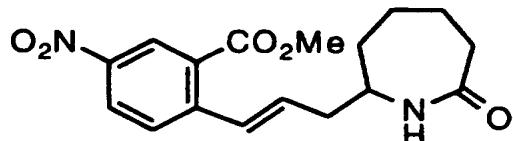
20

The Isomer B title material of Example 18 in acetonitrile is coupled to methyl-2-bromo-5-nitrobenzoate (Aldrich) in the presence of palladium acetate, tri-o-tolylphosphine, and triethylamine by the method of Example 32 to provide

25   the title material as either or both the Z and E isomers.

Example 160

methyl 5-nitro-2-[3-(3,4,5,6-tetrahydro-7-methoxy-2H-
azepin-2-yl)-1-propenyl]benzoate

5
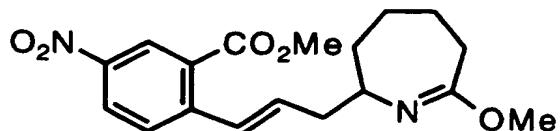
The product of Example 159 is reacted with
trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the
10   method of Example 3 to produce the title material.

Example 161

15   methyl 2-[3-(hexahydro-7-imino-1H-azepin-2-yl)-1-
propenyl]-5-nitrobenzoate, monohydrochloride
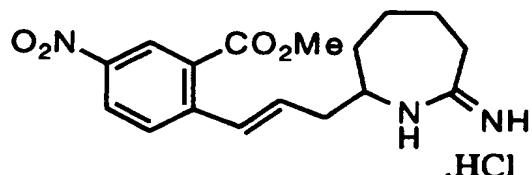
20   The product of Example 160 is reacted with ammonium
chloride by the method of Example 5 to generate the title
compound.

25   Example 162
methyl 5-amino-2-[3-(hexahydro-7-imino-1H-azepin-2-yl)-1-
propenyl]benzoate, dihydrochloride
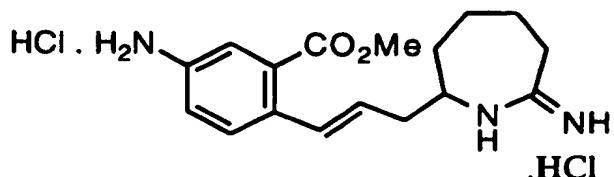
The title material of Example 161 in MeOH is hydrogenated
over Pd on carbon in a standard Parr apparatus
selectively reducing the nitro function to generate the
title product.

5

Example 163

hexahydro-7-[2-(3-methoxyphenyl)ethenyl]-2H-azepin-2-one

10
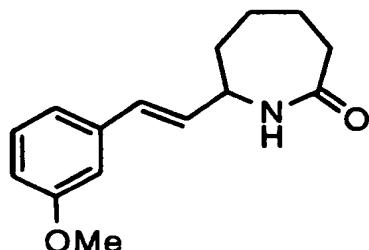
The Isomer A title material of Example 78 in acetonitrile
is coupled to 3-bromo-anisole (Aldrich) in the presence
palladium acetate, tri-o-tolylphosphine, and
triethylamine by the method of Example 32 to provide the
title material as either or both the Z and E isomers.

15

20   Example 164

3,4,5,6-tetrahydro-7-methoxy-2-[2-(3-
methoxyphenyl)ethenyl]-2H-azepine

25
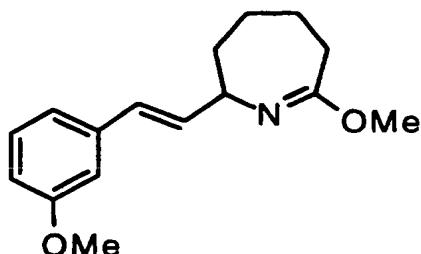
The product of Example 163 is reacted with
trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the
method of Example 3 to produce the title material.

5

Example 165

hexahydro-7-[2-(3-methoxyphenyl)ethenyl]-2H-azepin-2-
imine, monohydrochloride

10
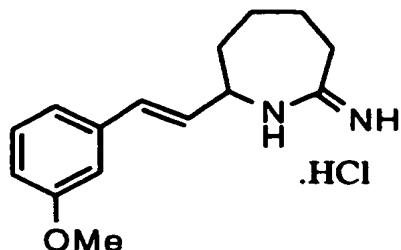
The product of Example 164 is reacted with ammonium
chloride by the method of Example 5 to generate the title
15 compound.

Example 166

20 hexahydro-7-[2-(3-methoxyphenyl)ethyl]-2H-azepin-2-one
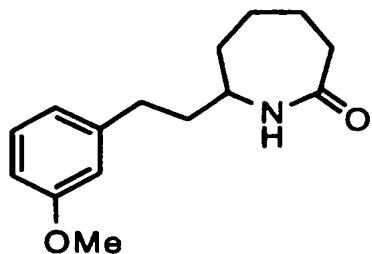
The title material of Example 163 in MeOH is hydrogenated
25 over Pd on carbon in a standard Parr apparatus by the
method of Example 35 to generate the title product.

Example 167

3,4,5,6-tetrahydro-7-methoxy-2-[2-(3-
methoxyphenyl)ethyl]-2H-azepine

5
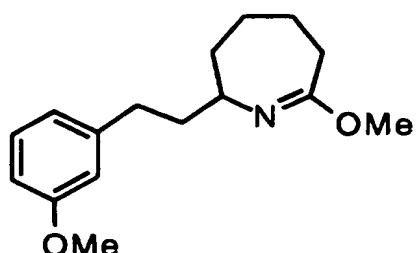
The product of Example 166 is reacted with
trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the
10   method of Example 3 to produce the title material.

Example 168

15   hexahydro-7-[2-(3-methoxyphenyl)ethyl]-2H-azepin-2-imine,
monohydrochloride
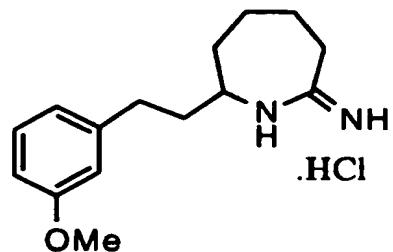
20   The product of Example 167 is reacted with ammonium
chloride by the method of Example 5 to generate the title
compound.

Example 169

7-[2-(3-furanyl)ethenyl]hexahydro-2H-azepin-2-one

5
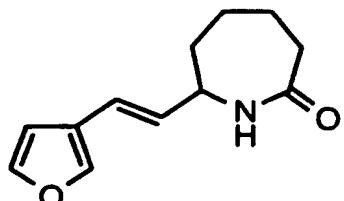
The Isomer A title material of Example 78 in acetonitrile
is coupled to 3-bromo-furan (Aldrich) in the presence
palladium acetate, tri-o-tolylphosphine, and
10   triethylamine by the method of Example 32 to provide the
title material as either or both the Z and E isomers.

Example 170

15

7-[2-(3-furanyl)ethyl]hexahydro-2H-azepin-2-one
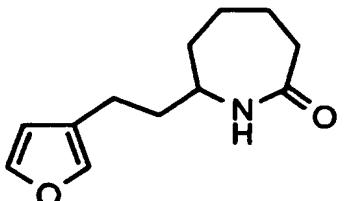
20   The title material of Example 169 in MeOH is hydrogenated
over Pd on carbon in a standard Parr apparatus by the
method of Example 35 to generate the title product.

Example 171

3,4,5,6-tetrahydro-2-[2-(3-furanyl)ethyl]-7-methoxy-2H-azepine

5
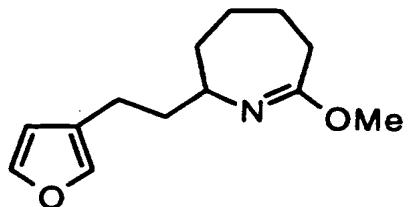
The product of Example 170 is reacted with trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the

10   method of Example 3 to produce the title material.

Example 172

15   7-[2-(3-furanyl)ethyl]hexahydro-2H-azepin-2-imine, monohydrochloride
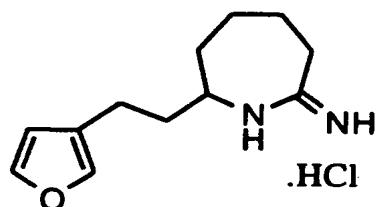
20   The product of Example 171 is reacted with ammonium chloride by the method of Example 5 to generate the title compound.

Example 173

hexahydro-7-[2-(2-thienyl)ethenyl]-2H-azepin-2-one

5
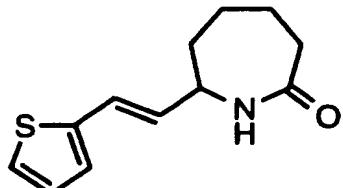
The Isomer A title material of Example 78 in acetonitrile
is coupled to 2-bromothiophene (Aldrich) in the presence
palladium acetate, tri-o-tolylphosphine, and
10   triethylamine by the method of Example 32 to provide the
title material as either or both the Z and E isomers.

Example 174

15

3,4,5,6-tetrahydro-7-methoxy-2-[2-(2-thienyl)ethyl]-2H-
azepine

20
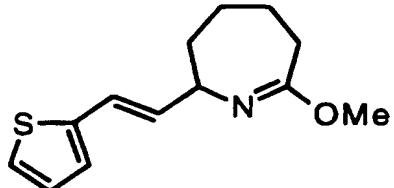
The product of Example 173 is reacted with
trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the
method of Example 3 to produce the title material.

Example 175

hexahydro-7-[2-(2-thienyl)ethenyl]-2H-azepin-2-imine,
monohydrochloride

5
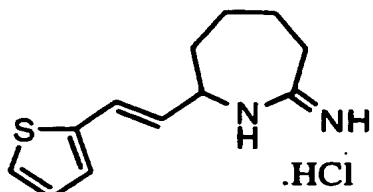
The product of Example 175 is reacted with ammonium
chloride by the method of Example 5 to generate the title
10 compound.

Example 176

15 hexahydro-7-[2-(2-thienyl)ethyl]-2H-azepin-2-imine,
monohydrochloride
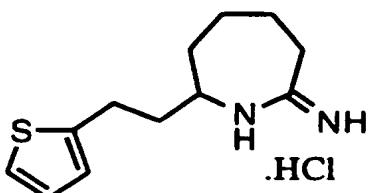
20 The title material of Example 175 in EtOH is hydrogenated
over 10% Pd on carbon catalyst in a standard Parr
apparatus by the method of Example 35 to generate the
title product.

Example 177

methyl 5-[3-(hexahydro-7-oxo-1H-azepin-2-yl)-1-
propenyl]furan-2-carboxylate

5
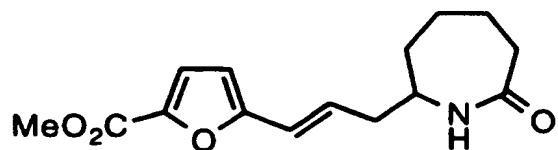
The Isomer B title material of Example 18 in acetonitrile
is coupled to methyl 5-bromo-furanate, prepared from 5-
10   bromofuroic acid (Aldrich) and thionyl chloride in
methanol, in the presence of palladium acetate, tri-o-
tolylphosphine, and triethylamine by the method of
Example 32 to provide the title material as either or
both the Z and E isomers.

15

Example 178

methyl 5-[3-(3,4,5,6-tetrahydro-7-methoxy-2H-azepin-2-
20   yl)-1-propenyl]furan-2-carboxylate
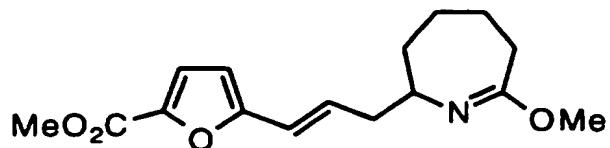
The product of Example 177 is reacted with
25   trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the
method of Example 3 to produce the title material.

Example 179

methyl 5-[3-(hexahydro-7-imino-1H-azepin-2-yl)-1-
propenyl]furan-2-carboxylate, monohydrochloride

5
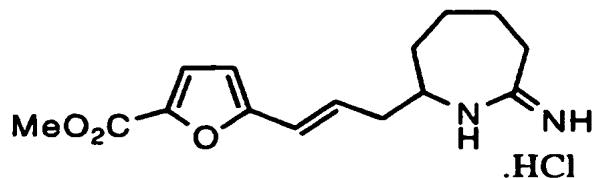
The product of Example 178 is reacted with ammonium
chloride by the method of Example 5 to generate the title

10   compound.

Example 180

15   methyl 5-[3-(hexahydro-7-imino-1H-azepin-2-
      yl)propyl]furan-2-carboxylate, monohydrochloride
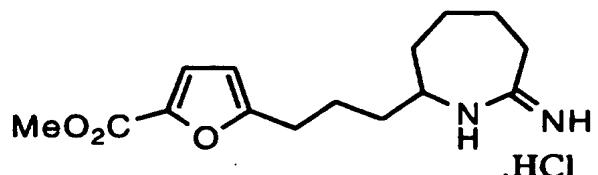
20   The title material of Example 179 in EtOH is hydrogenated
      over 10% Pd on carbon catalyst in a standard Parr
      apparatus by the method of Example 35 to generate the
      title product.

Example 181

hexahydro-7-[2-(2-thiazolyl)ethenyl]-2H-azepin-2-one

5
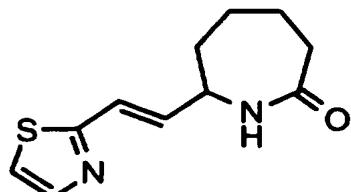
The Isomer A title material of Example 78 in acetonitrile
is coupled to 2-bromothiazole (Aldrich) in the presence
of palladium acetate, tri-o-tolylphosphine, and
10   triethylamine by the method of Example 32 to provide the
title material as either or both the Z and E isomers.

Example 182

15

3,4,5,6-tetrahydro-7-methoxy-2-[2-(2-thiazolyl)ethenyl]-
2H-azepine

20
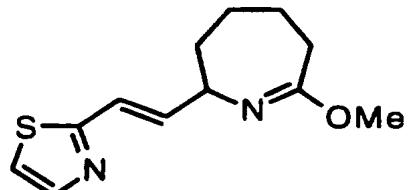
The product of Example 181 is reacted with one equivalent
of trimethyloxonium tetrafluoroborate in CH2Cl2 by the
method of Example 3 to produce a mixture of the title
material and the N-methylated thiazolium salt which is
25   isomerized on heating to the title material.

Example 183

hexahydro-7-[2-(2-thiazolyl)ethenyl]-2H-azepin-2-imine,
monohydrochloride

5
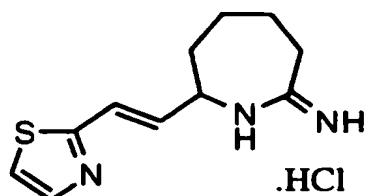
The product of Example 182 is reacted with ammonium
chloride by the method of Example 5 to generate the title
10   compound.

Example 184

15   hexahydro-7-[2-(2-thiazolyl)ethyl]-2H-azepin-2-imine,
monohydrochloride
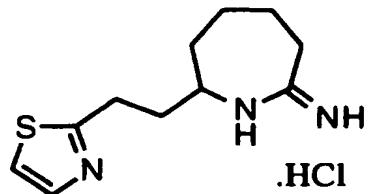
20   The title material of Example 183 in EtOH is hydrogenated
over 10% Pd on carbon catalyst in a standard Parr
apparatus by the method of Example 35 to generate the
title product.

Example 185

1,1-dimethylethyl hexahydro-2-oxo-7-(phenylmethyl)-1H-
azepine-1-carboxylate

5
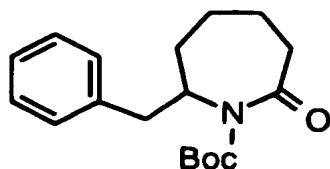
To the Isomer-A title product of Example 2 in dry THF
maintained under an Ar atmosphere is added
10   dimethylaminopyridine (DMAP). di-t-butyl dicarbonate in
THF is then added and the reaction mixture is brought to
reflux. After cooling the reaction to room temperature,
all solvent is removed under reduced pressure and the
title material is isolated by HPLC.

15

Example 186

1.1-dimethylethyl hexahydro-2-oxo-7(phenylmethyl)-3-
20   (phenylseleno)-1H-azepine-1-carboxylate
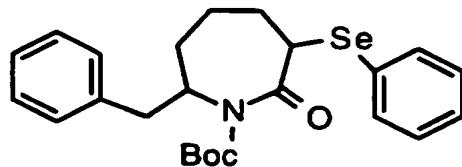
To a stirring solution of the product of Example 185 in
25   THF at -78 °C is added lithium hexamethyldisilazide also
in THF. After stirring the solution at -78 °C,
benzeneselenyl chloride is added. The reaction is
stirred cold, warmed to room temperature and stirred at
this temperature. The mixture is then diluted with Et_2O,
30   partitioned between water and brine, and the title
product isolated from the organic layer by HPLC.

Example 187

1,5,6,7-tetrahydro-7-(phenylmethyl)-2H-azepin-2-one
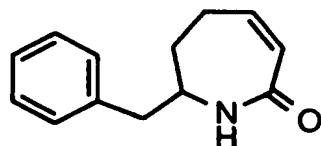
187 A) The product of Example 186 in THF is treated with 30% hydrogen peroxide (H2O2). All solvent is removed under reduced pressure and the unsaturated product, 1,1-dimethylethyl 1,5,6,7-tetrahydro-2-oxo-7-(phenylmethyl)-2H-azepine-1-carboxylate, is purified by HPLC methods.
187) The Boc protected product of this Example part A is dissolved in acetic acid and treated with a 4N solution of HCl in dioxane. All solvent is removed under reduced pressure and the title material purified by HPLC methods.

Example 188

3,4-dihydro-7-methoxy-2-(phenylmethyl)-2H-azepine
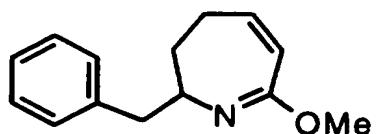
The product of Example 187 is reacted with one equivalent of trimethyloxonium tetrafluoroborate in CH2Cl2 by the method of Example 3 to produce the title material.

Example 189

1,5,6,7-tetrahydro-7-(phenylmethyl)-2H-azepin-2-imine,
monohydrochloride
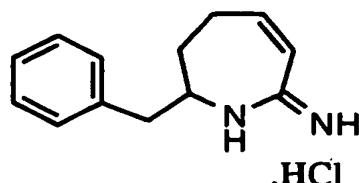


The product of Example 188 is reacted with ammonium
chloride by the method of Example 5 to generate the title
compound.

Example 190

2-[(4,5-dihydro-3-phenylisoxazolyl-5-yl)methyl]-3,4,5,6-
tetrahydro-7-methoxy-2H-azepine
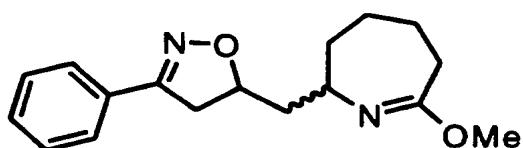
To a magnetically stirred slurry of trimethyloxonium
tetrafluoroborate (Sigma, 0.13 g, 0.9 mmol) and CH_2Cl_2
(10 mL) under nitrogen (N_2) was added the Isomer-B
product of Example 125 (0.22 g, 0.81 mmol). This mixture
was stirred at room temperature for 18 hours before it
was diluted with 30 mL of EtOAc and partitioned between
the organic layer and 40 mL of saturated $NaHCO_3$. The
organic phase was separated, dried over $MgSO_4$, filtered,
and stripped of all solvent under reduced pressure to
provide 0.17 g (73%) of the crude title product as a pale
yellow oil. This material was used as is in subsequent
Example 191.

Example 191

7-[(4,5-dihydro-3-phenylisoxazolyl-5-yl)methyl]hexahydro-
2H-azepine-2-imine, monotrifluoroacetic acid salt

$$CF_3CO_2H$$
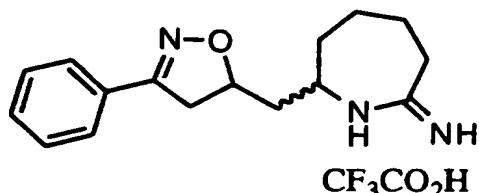
The title product of Example 190 (0.17 g, 0.6 mmol) and
0.035 g (0.65 mmol) of NH4Cl were refluxed in 10 mL of
MeOH under a N_2 atmosphere for 18 h. After cooling the
reaction to room temperature, it was filtered and
partitioned between 15 mL of water and 7 mL of EtOAc.
The organic and aqueous phases were separated and the
aqueous phase was extracted with a 15 mL portion of EtOAc
before it was lyophilized to provide 0.13 g (71%) of an
orange solid material. Chromatography of 0.1 g on a
preparatory C-18 column eluting with acetonitrile/water
afforded after lyophilization from trifluoroacetic acid
(TFA)/ water 0.04 g of the title compound as an off-white
solid material.

1H NMR(D_2O): d 7.6 (d, 2H), 7.4 (m, 3H), 4.85 (m, 1H),
3.75 (m, 1H), 3.6 (dd, 1H), 3.15 (dd, 1H) 2.65 (m, 1H),
2.5 (m, 1H), 2.0-1.3 (m, 8H). M+H = 272.

Example 192

The following functionalized aromatic methyl halides and
equivalents are reacted with cyclohexanone by the process
described in Example 65. The resulting 2-[(substituted
aromatic)methyl]cyclohexanone is treated with
hydroxylamine as described in Example 1 to yield the
corresponding oxime, which is then treated as described in
Example 2 to give a mixture of 3- and 7-substituted

caprolactams. They are separated as also described in
Example 2, and then individually treated as described in
Example 3 to yield the corresponding imino ether. This
imino ether is treated with ammonium chloride in methanol
5   as described in Example 5 to give the desired product
amidines:

STARTING HALIDE	CORRESPONDING PRODUCT
α-bromo-2,6-dichlorotoluene	7-[(2,6-dichlorophenyl)methyl]-hexahydro-2H-azepin-2-imine
α-bromo-4-fluorotoluene	7-[(4-fluorophenyl)methyl]hexa-hydro-2H-azepin-2-imine
α-bromo-2,4-difluorotoluene	7-[(2,4-difluorophenyl)methyl]-hexahydro-2H-azepin-2-imine
α-bromo-2,3,4,5,6-pentafluoro-toluene	7-[(2,3,4,5-pentafluorophenyl)-methyl]hexahydro-2H-azepin-2-imine
α-bromo-4-trifluoromethyl-toluene	hexahydro-7-[[4-(trifluoro-methyl)phenyl]methyl]-2H-azepin-2-imine
α-bromo-3-trifluoromethyl-toluene	hexahydro-7-[[3-(trifluoro-methyl)phenyl]methyl]-2H-azepin-2-imine
2-(bromomethyl)biphenyl	7-[(2-biphenylyl)methyl]hexa-hydro-2H-azepin-2-imine

α-bromo-2-nitrotoluene	hexahydro-7-[(2-nitrophenyl)-methyl]-2H-azepin-2-imine
α-bromo-4-nitrotoluene	hexahydro-7-[(4-nitrophenyl)-methyl]-2H-azepin-2-imine
α-bromo-4-carboxymethyl-toluene	4-[(hexahydro-7-imino-2H-azepin-2-yl)methyl]benzene-acetic acid
2-chloro-5-(chloromethyl)thiophene	7-[(5-chlorothien-2-yl)methyl]-hexahydro-2H-azepin-2-imine
4-(chloromethyl)-3,5-dimethylisoxazole	7-[(3,5-dimethylisoxazol-4-yl)methyl]hexahydro-2H-azepin-2-imine

Example 193

5   2-[(tetrahydro-2H-pyran-2-yl)methyl]cyclohexanol
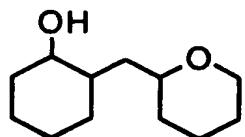
To a stirring THF solution of the Grignard reagent
10   (formed from 2-(bromomethyl)tetrahydro-2H-pyran, 16 mmol,
and powdered magnesium, 20 milligram-atoms) and cooled to
-30 °C, CuI is added as a *bolus*. After approx. 10 min.,
a solution of cyclohexene oxide (10 mmol) is added
slowly, maintaining the reaction temperature below -25 °C
15   until the addition is complete. The mixture is then
stirred at 0 °C for 2 hours and checked by TLC and/or GC.
The reaction is quenched by pouring into concentrated

NH4Cl solution (if starting material remains, the
reaction may be warmed to r.t. and followed by TLC or GC
until no additional starting material is observed).
Also, the addition of some concentrated NH4OH solution

5   combined with vigorous stirring may be used to remove
suspended CuI from the mixture. This mixture is then
extracted with 2 portions of ether or 1:1 EA-hexane. The
combined extracts are then washed with brine and dried
(MgSO4). The product may be sufficiently pure at this

10   point for use in the next reaction. Otherwise, it may be
purified by distillation or flash chromatography.

Example 194

15

2-[(tetrahydro-2H-pyran-2-yl)methyl]cyclohexanone
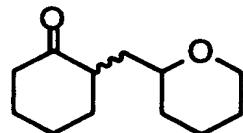
20   Neat, dry DMSO (4 equivalents) is added slowly to a
CH2Cl2 solution of the oxalyl chloride (1.25 equivalents)
cooled to -70 °C under N2. After stirring for about 15
min., the product of Example 193 (1 equivalent) in CH2Cl2
is added slowly. Neat triethylamine (4 equivalents) is

25   then added and the mixture is warmed to 0 °C. After 30
min., the mixture is poured into stirred ice-water and
neutralized with dilute HCl. The mixture is then
separated and the aqueous layer extracted with CH2Cl2.
The organic extracts are then combined, washed with

30   dilute brine, dried (MgSO4) and stripped of all solvent
under reduced pressure. The crude title compound is
purified by column chromatography.

Example 195

hexahydro-7-[(tetrahydro-2H-pyran-2-yl)methyl]-1H-azepin-
2-imine monohydrochloride

.HCl
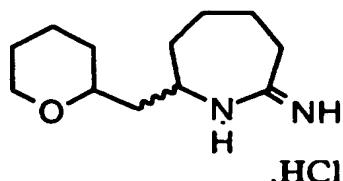
The product of Example 194 is converted to the
corresponding oxime by the methods taught in Example 39,
and then to the corresponding mixture of lactams as
taught in Example 67. The mixture of lactams is
separated as also described in Example 67. The resulting
3-substituted caprolactam is reserved for use as
described in Example 196 (vide infra), and the 7-
substituted caprolactam is treated with trimethyloxonium
tetrafluoroborate as described in Example 3 to give the
corresponding imino ether. This imino ether is treated
with NH4Cl in methanol as described in Example 5 to give
the title compound.

Example 196

hexahydro-3-[(tetrahydro-2H-pyran-2-yl)methyl]-2H-azepin-
2-imine

.HCl
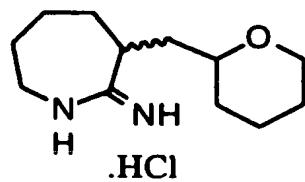
The 3-[(2-tetrahydropyanyl)methyl]caprolactam isolated in
Example 195 is treated as described in Example 3 to give
the corresponding imino ether, and then with NH4Cl in

methanol as described in Example 5 to give the title compound.
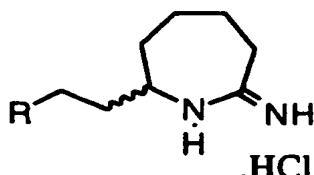
Example 197

A) R = phenyl
B) R = p-nitrophenyl
C) R = p-methoxyphenyl

The aromatic ethyl halides listed below as STARTING HALIDE are reacted with cyclohexene oxide by the process described in Example 193. The resulting 2-(aromatic-ethyl) cyclohexanols are then oxidized to the respective 2-(aromatic-ethyl) cyclohexanones by the method of Example 194. The 2-(aromatic-ethyl) cyclohexanones are treated with hydroxylamine as taught in Example 1 to yield the corresponding oxime, which is then treated as described in Example 2 to give a mixture of 3- and 7-substituted caprolactams. This mixture is separated also as described in Example 2, and then individually treated as taught in Example 3 to yield the corresponding imino ether. The imino ethers are treated with ammonium chloride in methanol as described in Example 5 to give the desired product amidines described below:

STARTING HALIDE	CORRESPONDING PRODUCT
A) (2-bromoethyl)benzene	hexahydro-7-(2-phenylethyl)-1H-azepin-2-imine, monohydrochloride
B) (2-bromoethyl)-4-nitrobenzene	hexahydro-7-[2-(4-nitrophenyl)e 1H-azepin-2-imine, monohydrochloride
C) (2-bromoethyl)-4-methoxybenzene	hexahydro-7-[2-(4-methoxyphenyl ethyl]-1H-azepin-2-imine, monohydrochloride

Example 198

7-[3-[5-(1,3-dioxolan-2-yl)thien-2-yl)-2-
propenyl]hexahydro-2H-azepin-2-imine, monohydrochloride
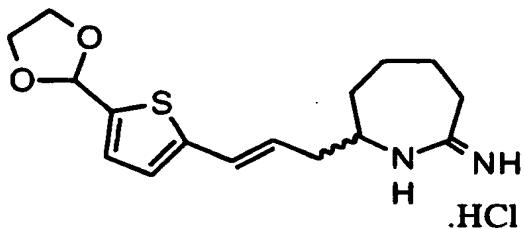
Example 198 A)   The Isomer B title material of Example 18
in acetonitrile is coupled to 2-(5-bromo-2-
thienyl)dioxolane in the presence palladium acetate, tri-
o-tolylphosphine, and triethylamine by the method of
Example 32 to provide 7-[3-[5-(1,3-dioxolan-2-yl)thien-2-
yl]-2-propenyl]hexahydro-1H-azepin-2-one as primarily the
E isomer.

Example 198 B)   The product of part A above is reacted
with trimethyloxonium tetrafluoroborate by the method of
Example 67 to yield imino ether, 2-[3-[5-(1,3-dioxolan-2-
yl)thien-2-yl]propyl]-3,4,5,6-tetrahydro-7-methoxy-2H-
azepine.

Example 198)   the crude product of part B above is
reacted with ammonium chloride in methanol by the method
of Example 5 to give the title material after reverse
phase chromatographic purification.

Example 199

5-[3-(hexahydro-7-imino-1H-azepin-2-yl)-1-
propenyl]thiophene-2-carboxamide, monohydrochloride
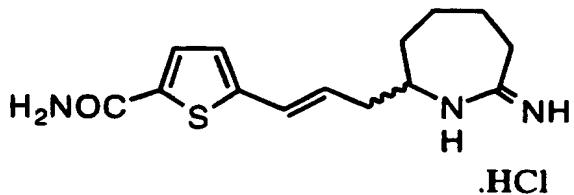
5

Example 199 A)   A sample of the product of part A,
Example 198, 7-[3-[5-(1,3-dioxolan-2-yl)thien-2-yl]-2-
propenyl]hexahydro-1H-azepin-2-one, is treated with

10   dilute HCl to generate aldehyde, 5-[3-(hexahydro-7-oxo-
1H-azepin-2-yl)-1-propenyl]thiophene-2-carboxaldehyde.
Example 199 B)   The product of this Example, part A
above, is oxidized to 5-[3-(hexahydro-7-oxo-1H-azepin-2-
yl)-1-propenyl]thiophene-2-carboxylic acid using

15   potassium permanganate solubilized in benzene with
dicyclohexyl-18-crown-6 by the method described by D. J.
Sam et al *J. Am. Chem. Soc.* **1972**, 94, 4024.
Example 199 C)   To a cold solution of thionyl chloride in
methanol is added the product of this Example, part B

20   above.   The product methyl ester, methyl 5-[3-(hexahydro-
7-oxo-1H-azepin-2-yl)-1-propenyl]thiophene-2-carboxylate,
is isolated after quenching the reaction with $KHCO_3$,
extracting with EtOAc, and purifying by column
chromatography.

25   Example 199 D)   The product of this Example, part C
above, is reacted with trimethyloxonium tetrafluoroborate
by the method of Example 67 to yield imino ether, methyl
5-[3-(3,4,5,6-tetrahydro-7-methoxy-2H-azepin-2-yl)-1-
propenyl]thiophene-2-carboxylate.

30   Example 199 E)   The crude product of this Example, part D
above, is reacted with ammonium chloride in methanol by
the method of Example 5 to give the amidine, methyl 5-[3-
(hexahydro-7-imino-1H-azepin-2-yl)-1-propenyl]thiophene-
2-carboxylate, monohycrochloride.

Example 199 F)   The product of this Example, part E
above, is hydrolyzed to its free acid, 5-[3-(hexahydro-7-
imino-1H-azepin-2-yl)-1-propenyl]thiophene-2-carboxylic
acid, monohydrochloride using HCl.

Example 199)   The product of this Example, part F above,
is reacted with isobutylchloroformate in the presence of
N-methylmorpholine followed by ammonium chloride to
provide the title product after reverse phase
chromatographic purification.

Example 200

methyl 2-[3-(hexahydro-7-imino-1H-azepin-2-yl)-1-
propenyl]-5-methoxybenzoate, monohydrochloride
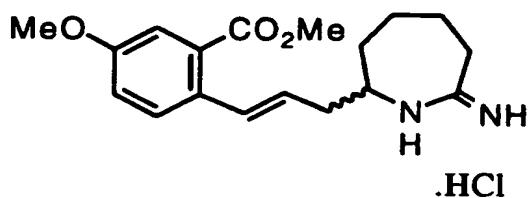
Example 200 A)   The Isomer B title material of Example 18
in acetonitrile is coupled to methyl 2-bromo-5-
methoxybenzoate in the presence of palladium acetate,
tri-o-tolylphosphine, and triethylamine by the method of
Example 32 to provide methyl 2-[3-(hexahydro-7-oxo-1H-
azepin-2-yl)-1-propenyl]-5-methoxybenzoate as primarily
its E isomer.

Example 200 B)   The product of this Example, part A
above, is reacted with trimethyloxonium tetrafluoroborate
by the method of Example 67 to yield imino ether, methyl
2-[3-(3,4,5,6-tetrahydro-7-methoxy-2H-azepin-2-yl)-1-
propenyl]-5-methoxybenzoate.

Example 200)   The crude product of this Example, part B
above, is reacted with ammonium chloride in methanol by
the method of Example 5 to give the title material after
reverse phase chromatographic purification.

Example 201

β-(2-oxocyclohexyl)-4-methylbenzenepropanoic acid
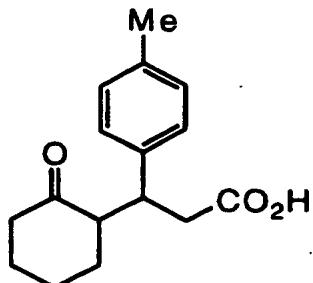
5

1-pyrrolidino-1-cyclohexene is refluxed with methyl a-(2-oxocyclohexyl)benzenepropanoate in dimethylformamide (DMF) for 24 hours and refluxing is continued for another hour after the addition of water. DMF is removed under
10   reduced pressure and the residue is diluted with water and extracted three times with EtOAc. The combined EtOAc extracts are washed with 1N HCl and then with brine. The organic phase is dried over MgSO$_4$ and evaporated to give crude methyl b-(2-oxocyclohexyl)-4-
15   methylbenzenepropanoate. This material is treated with 1 N LiOH/methanol to give the title material.

Example 202

20   Isomer A: hexahydro-b-(4-methylphenyl)-7-oxo-1H-azepine-2-propanoic acid
        Isomer B: hexahydro-b-(4-methylphenyl)-2-oxo-1H-azepine-3-propanoic acid

25
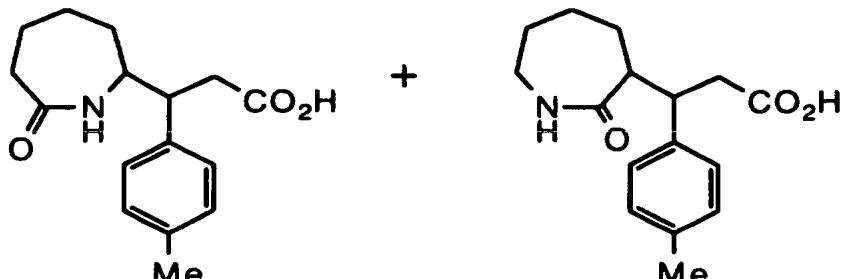
Isomer A   Isomer B

The title material of Example 201 in formic acid is added
to a solution of hydroxylamine-O-sulfonic acid in formic
acid over a 5 min. period with stirring under N_2. The

5   mixture is heated under reflux for 3 hours and then
cooled to room temperature. The reaction is quenched
with cold water and the solution is neutralized with 6N
NaOH. It is then extracted three times with CH_2Cl_2. The
combined organic layers are dried over $MgSO_4$ and the

10   solvent is removed on a rotary evaporator. The desired
products are purified and isolated by HPLC to give both
the 3- and 7- substituted title products.

15   Example 203

Isomer A: methyl hexahydro-7-imino-b-(4-methylphenyl)-
1H-azepine-2-propanoate, monohydrochloride
Isomer B: methyl hexahydro-2-imino-b-(4-methylphenyl)-

20   1H-azepine-3-propanoate, monohydrochloride
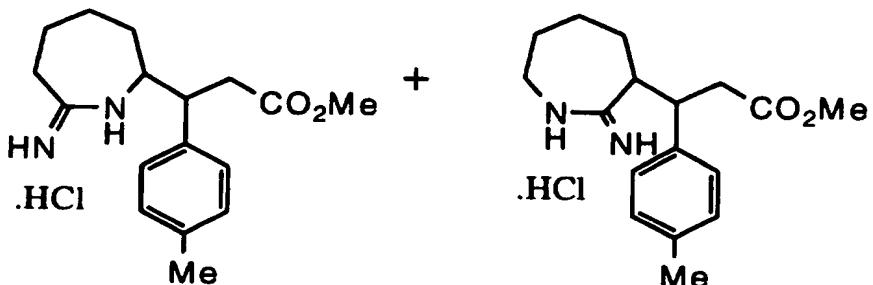
Each of the title caprolactams of Example 202 is

25   independently treated as described in Example 3 to yield
the corresponding imino ethers. The imino ethers are
then treated with ammonium chloride in methanol as
described in Example 5 to give the desired amidines.

Example 204

The following activated vinyl derivatives are reacted
with 1-pyrrolidino-1-cyclohexene following the method
5   described in Example 201. The resulting 2-substituted
cyclohexanone is treated with a solution of
hydroxylamine-O-sulfonic acid in formic acid as described
in Example 202 to give a mixture of 3- and 7-substituted
caprolactams. These lactams are treated as described in
10   Example 3 to yield the corresponding imino ether. This
imino ether is treated with ammonium chloride in methanol
as described in Example 5 to give the desired amidine
products illustrated below.

15   Example 204 A) methyl 3-[4-
(trifluoromethyl)phenyl]propenoate

        methyl hexahydro-7-imino-b-[4-
(trifluoromethyl)phenyl]-1H-azepine-2-propanoate,
20   monohydrochloride

A)
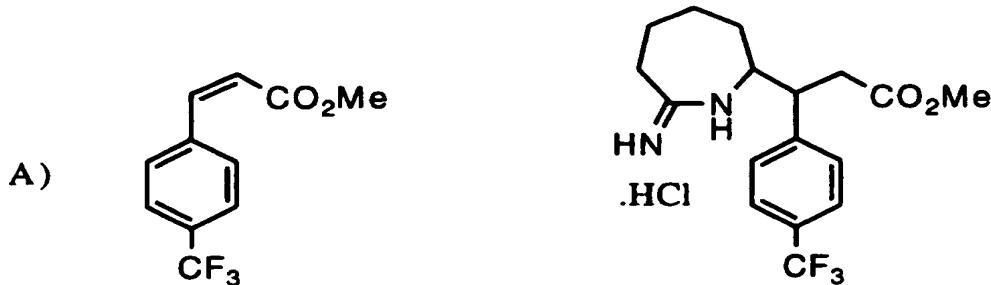
Example 204 B) (2-nitroethenyl)benzene

        hexahydro-7-(2-nitro-1-phenylethyl)-2H-azepin-2-
25   imine, monohydrochloride

B)

Example 204 C) 3-(2-furanyl)propenenitrile

b-(2-furanyl)hexahydro-7-imino-1H-azepine-2-propanenitrile, monohydrochloride

C)
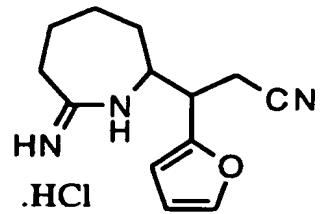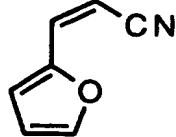
5   Example 204 D) methyl 3-(2-furanyl)propenoate

methyl β-(2-furanyl)hexahydro-7-imino-1H-azepine-2-propanoate, monohydrochloride

D)
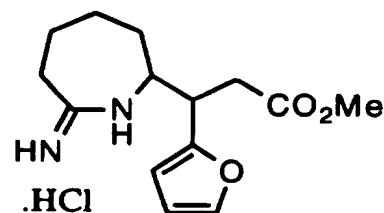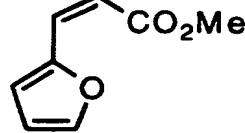
10   Example 204 E) (ethenylsulfonyl)benzene

hexahydro-7-[2-(phenylsulfonyl)ethyl]-2H-azepin-2-imine, monohydrochloride

E)

15
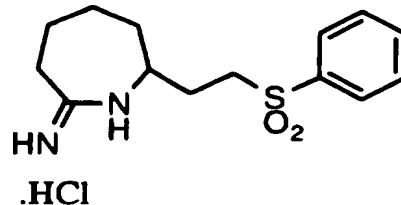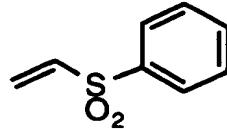
Example 205

hexahydro-7-imino-β-phenyl-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt

5
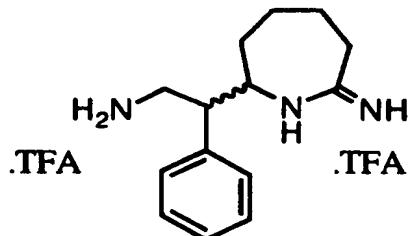
The product of Example 253 (350 mg; 1.3 mmol) was reduced via catalytic hydrogenation to afford 230 mg (75% yield)
10 of the title product as a white solid.
Mass spectral analysis for $C_{14}H_{21}N_3$: $M^+H = 232$

^1H NMR (D_2O): δ 7.40-7.20 (m,5H); 3.90-3.80 (m,1H); 3.50-3.35 (m,1H); 3.30-3.05 (m,2H); 2.80-2.40 (m,2H); 1.80-
15 1.00 (m,6H)

Example 206

20 N-[2-(hexahydro-7-imino-1H-azepin-2-yl)-2-phenylethyl]methanesulfonamide, monohydrochloride
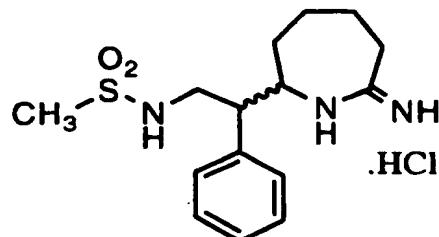
25 Example 206 A) The nitro function of the 7-substituted lactam generated in Example 204, reaction B, hexahydro-7-(2-nitro-1-phenylethyl)-1H-azepin-2-one, is reduced to an amine, 7-(2-amino-1-phenylethyl) hexahydro-1H-azepin-2-one, monohydrochloride, by the method of Example 205.

Example 206 B)   The product of this Example, part A is treated with an equivalent of methanesulfonyl chloride in the presence of triethylamine to yield its sulfonamide derivative, N-[2-(hexahydro-7-oxo-1H-azepin-2-yl)-2-
5   phenyl]methanesulfonamide.

Example 206 C)   The sulfonamide material of this Example, part B, is treated with trimethyloxonium tetrafluoroborate (1.5 equivalents) in CH2Cl2 following the method of Example 3 to give the iminoether
10   intermediate, N-[2-phenyl-2-(3,4,5,6-tetrahydro-7-methoxy-2H-azepin-2-yl)ethyl]methanesulfonamide.

Example 206)   The crude product of this Example, part C, is then treated with ammonium chloride in methanol following the method of Example 5 to give the title
15   compound.

Example 207

20   γ-(2-furanyl)hexahydro-7-imino-1H-azepine-2-propanamine, dihydrochloride
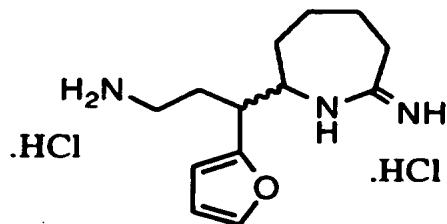
25   The product of Example 204, reaction C, b-(2-furanyl)hexahydro-7-imino-1H-azepine-2-propanenitrile, monohydrochloride, is reduced with H2 in a standard Parr hydrogenation apparatus using a Pd catalyst on a carbon support by the method described by J. A. Secrist et al *J.*
30   *Org. Chem.* **1972**, 37, 335.

Example 208

N-[3-(2-furanyl)-3-(hexahydro-7-imino-1H-azepin-2-
yl)propyl]methanesulfonamide, monohydrochloride

5
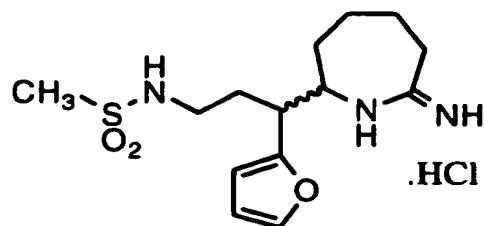
Example 208 A) The cyano function of the 7-substituted
lactam generated in Example 204, reaction C, b-(2-
10   furanyl)hexahydro-7-oxo-1H-azepinepropanenitrile, is
reduced to its amine, g-(2-furanyl)hexahydro-7-oxo-1H-
azepinepropanamine, monohydrochloride, by the method of
Example 207.

Example 208 B) The product of this Example, part A is
15   treated with an equivalent of methanesulfonylchloride in
the presence of triethylamine to yield its sulfonamide
derivative, N-[3-(2-furanyl)-3-(hexahydro-7-oxo-1H-
azepin-1-yl)propyl]methanesulfonamide.

Example 208 C) The sulfonamide material of this Example,
20   part B, is treated with trimethyloxonium
tetrafluoroborate (1.5 equivalents) in CH2Cl2 following
the method of Example 3 to give the iminoether
intermediate, N-[3-(2-furanyl)-3-(hexahydro-7-oxo-1H-
azepin-1-yl)propyl]methanesulfonamide.

25 Example 208) The crude product of this Example, part C,
is then treated with ammonium chloride in methanol
following the method of Example 5 to give the title
compound.

Example 209

1,1-dimethylethyl hexahydro-2-(4-methoxy-4-oxo-2-butenyl)-7-oxo-1H-azepine-1-carboxylate
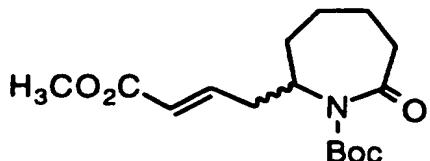
Example 209 A)   The title material of Example 18, isomer
B, is converted to its Boc derivative, 1,1-dimethylethyl
hexahydro-2-oxo-7-(2-propenyl)-1H-azepine-1-carboxylate,
by the method of Example 185.
Example 209 B) The Boc allyl lactam of this Example, part
A above, is dissolved in CH2Cl2, cooled to below -70 °C,
treated with ozone until a persistent blue color is
observed. After sparging with oxygen to remove excess
ozone, triphenylphosphine (1.5 equivalents) is added and
the mixture stirred at 0 °C for 30 minutes and then at
room temperature. overnight. The mixture is concentrated
and the residue is triturated with several volumes of
pentane to remove the phosphorous salts, filtered and
stripped to give a crude aldehyde, 1,1-dimethylethyl
hexahydro-2-(2-oxoethyl)-7-oxo-1H-azepine-1-carboxylate,
which is used without further purification in Part C
below.
Example 209) The crude aldehyde of this Example, part B
above, is dissolved in toluene and treated with 1.2
equivalents of methyl
(triphenylphosphoranylidene)acetate. The mixture is
refluxed for four hours. After cooling, the mixture is
concentrated and the residue is triturated with several
volumes of pentane to remove the phosphorous salts. The
extracts are filtered and stripped of all solvent. The
crude residue is then purified by column chromatography
to give the title product.

Example 210

methyl 1-[(1,1-dimethylethoxy)carbonyl]hexahydro-7-oxo-β-
(2-propenyl)-1H-azepine-2-butanoate

5
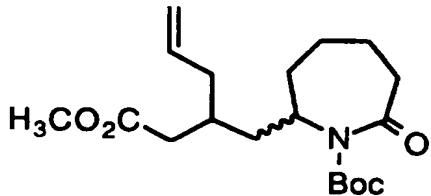
Four equivalents of allyl lithium are added to a stirring
suspension of 2 equivalents copper (I) iodide in THF at
10 -50 °C under argon. After the mixtures becomes
homogeneous (approx. 20 minutes.), a solution of the
title ester of Example 209 (1 equivalent) in THF is added
to the cold mixture and stirred below -50 °C for approx.
30 minutes. The mixture is poured into saturated
15 ammonium chloride solution and stirred vigorously for 15
minutes. The mixture is then partitioned between ether
and water and the organic layer is washed with water and
brine before it is dried (Na2SO4). The mixture is then
filtered and stripped of all solvent. The title material
20 is then purified by column chromatography.

Example 211

25 methyl 7-ethoxy-3,4,5,6-tetrahydro--β-(2-propenyl)-2H-
azepine-2-butanoate
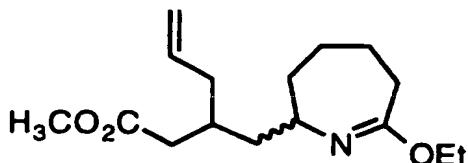
30 Example 211 A) The Boc group is removed from title
compound of Example 210 by the method of Example 199,

-153-

part A, to generate methyl hexahydro-7-oxo-b-(2-
propenyl)-1H-azepine-2-butanoate.
Example 211) This crude product of Example 211, part A,
is then treated with triethyloxonium tetrafluoroborate
5   (1.5 equivalents) in CH_2Cl_2 following the method of
Example 3 to give the title compound.

Example 212

10   methyl $-\beta$-(2,3-dihydroxypropyl)hexahydro-7-imino-1H-
azepine-2-butanoate, monohydrochloride
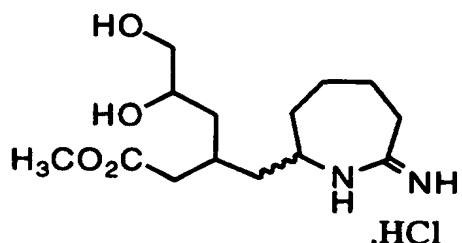
15   Example 212 A) The title product of Example 211
dissolved in a 1:1 mixture of acetone and water and
treated with osmium tetraoxide (2.5 equivalent %) and 4-
methylmorpholine oxide (2 equivalents) at room
temperature is allowed to stir overnight. The mixture is
20   then carefully neutralized with dilute HCl, concentrated
on a rotary evaporator, and extracted with 3 portions of
EtOAc. The combined organic extracts are then dried
(Na2SO4), stripped and purified by column chromatography
on silica gel to yield methyl b-(2,3-dihydroxypropyl)-7-
25   ethoxy-3,4,5,6-tetrahydro-2H-azepine-2-butanoate.
Example 212) The product of Example 211 part A is
treated with ammonium chloride in methanol following the
method of Example 5 to give the title compound.

Example 213

4-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]-3,4,5,6-
tetrahydro-6-hydroxymethyl-2H-pyran-2-one,

5   monohydrochloride
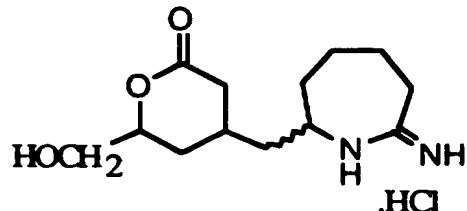
The amidine diol title product of Example 212   is

10   dissolved in 0.5 N HCl and warmed to 50 °C for 3 hours.
The excess water and acid are then removed by
lyophilization to give the title compound.

15   Example 214

hexahydro-7-[(4-morpholinyl)methyl]-2H-azepin-2-imine,
dihydrochloride

20
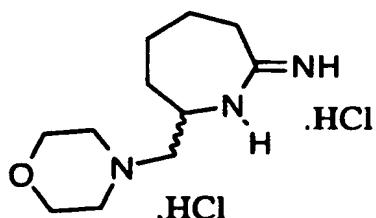
Example 214 A)   The title product of Example 78, Isomer-
A, is converted to its Boc derivative, 1,1-dimethylethyl
2-ethenylhexahydro-7-oxo-1H-azepine-1-carboxylate, by the

25   method of Example 185.
Example 214 B)   Treatment of the product of this Example,
part A above, with ozone as described in example 209,
part B, generates aldehyde product, 1,1-dimethylethyl 2-
formylhexahydro-7-oxo-1H-azepine-1-carboxylate.

Example 214 C)   The product of this Example, part B
above, in THF is reacted with morpholine in the presence
H₂ and a metal catalyst to yield, 1,1-dimethylethyl
hexahydro-2-[(4-morpholinyl)methyl]-7-oxo-1H-azepine-1-
5   carboxylate.
Example 214 D)   The Boc group is removed from the product
of this Example, part C above by the method of Example
199, part A, to generate hexahydro-7-[(4-
morpholinyl)methyl]-1H-azepin-2-one.
10   Example 214 E)   This product of this Example, part D
above is then treated with triethyloxonium
tetrafluoroborate (1.1 equivalents) in CH₂Cl₂ following
the method of Example 3 to give 7-ethoxy-3,4,5,6-
tetrahydro-2-[(4-morpholinyl)methyl]-2H-azepine.
15   Example 214)   The crude product of this Example, part E
above, is then reacted with ammonium chloride in methanol
following the method of Example 5 and then with dilute
HCl to produce the title compound.

20

Example 215

hexahydro-2-imino-7-[(4-morpholinyl)methyl]-1H-azepin-3-
ol, dihydrochloride
25
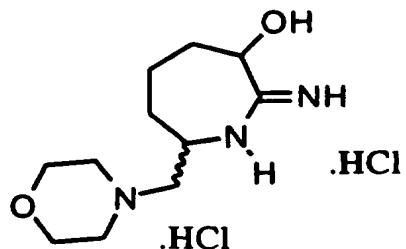
Example 215 A)   The product of Example 214, part A, 1,1-
dimethylethyl 2-ethenylhexahydro-7-oxo-1H-azepine-1-
30   carboxylate, is treated with an organo lithium base at
low temperature to generate the enolate which is
subsequently reacted with bis(trimethylsilyl)peroxide by
the methods of F. A. Davis et al *Tettrahodron Lett.*
1988, 29, 4269 and L. Camici et al *Tettrahodron Lett.*

1988, 29, 4197 to yield 1,1-dimethylethyl hexahydro-3-hydroxy-7-[(4-morpholinyl)methyl]-2-oxo-1H-azepine-1-carboxylate.

Example 215 B)   Removal of the Boc protecting group by
treatment of the product of this Example, part A above
with dilute HCl gives the lactam hexahydro-3-hydroxy-7-
[(4-morpholinyl)methyl]-1H-azepin-2-one.

Example 215 C)   The product of Example 215, part B is
treated with acetic anhydride in the presence of pyridine
to generate 3-acetyloxyhexahydro-7-[(4-
morpholinyl)methyl]-1H-azepin-2-one.

Example 215 D)   The product of this Example, part C above
is then treated with trimethyloxonium tetrafluoroborate
(1.5 equivalents) in CH2Cl2 by the method of Example 3 to
give 3,4,5,6-tetrahydro-7-methoxy-2-[(4-
morpholinyl)methyl]-2H-azepin-3-ol acetate.

Example 215)   The crude product of this Example, part D
above, is then reacted with ammonium chloride in methanol
following the method of Example 5 and then with dilute
HCl to produce the title compound.

Example 216

5-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]4,5-
dihydroisoxazol-3-amine, dihydrochloride
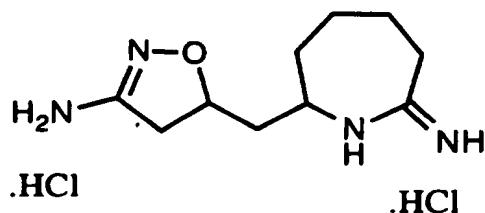
216 A) The title product isomer B of Example 18 (7-allyl
caprolactam) is reacted with ethyl chlorooximinoyl
acetate in toluene by the method of P. Caldirola, et.
al., Heterocycles **1985**, 23(10), 2479, to generate ethyl

5-[(hexahydro-7-oxo-1H-azepin-2-yl)methyl]-4,5-
dihydroisoxazole-3-carboxylate.

216 B) The crude product of this Example, part A above,
is hydrolyzed in aqueous HCl to generate 5-[(hexahydro-7-

5   oxo-1H-azepin-2-yl)methyl]-4,5-dihydroisoxazole-3-
carboxylic acid.

216 C) The crude product of this Example, part B above,
is reacted with diphenylphosphoryl azide and
triethylamine in benzene to generate 7-[(3-amino-4,5-

10   dihydroisoxazol-5-yl)methyl]hexahydro-1H-azepin-2-one,
monohydrochloride.

216 D) The crude product of this Example, part C above,
is reacted with di-tert-butyldicarbonate in aqueous
sodium hydroxide to generate 1,1-dimethylethyl [5-

15   [(hexahydro-7-oxo-1H-azepin-2-yl)methyl]-4,5-
dihydroisoxazol-3-yl]carbamate.

216 E) The crude product of this Example, part D above,
is reacted with trimethyloxonium tetrafluoroborate by the
method of Example 3 to generate the iminoether. The

20   iminoether is reacted with ammonium chloride by the
method of Example 5 to generate 1,1-dimethylethyl [5-
[(hexahydro-7-imino-1H-azepin-2-yl)methyl]-4,5-
dihydroisoxazol-3-yl]carbamate.

216) The crude product of this Example, part E above, is

25   reacted with HCl/dioxane to generate the title compound.

Example 217

30   5-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]-1-
methylpyrazolidin-3-one, dihydrochloride
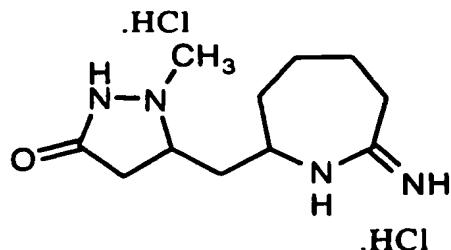
217 A) 1-morpholinocyclohexene is reacted with ethyl 4-bromocrotonate in 1,4-dioxane. The reaction mixture is diluted with water to generate ethyl 4-(2-oxocyclohexyl)-2-butenoate.

5 217 B) The crude product of this Example, part A above, is reacted with hydroxylamine-O-sulfonic acid to generate ethyl 4-(hexahydro-7-oxo-1H-azepin-2yl)-2-butenoate.

217 C) The crude product of this Example, part B above, is reacted with methylhydrazine to generate 7-[(4,5-

10 dihydro-3-hydroxy-1-methyl-1H-pyrazol-5-yl)methyl]hexahydro-1H-azepin-2-one.

217 D) The crude product of this Example, part C above, is reacted with acetic anhydride to generate 7-[[3-(acetyloxy)-4,5-dihydro-1-methyl-1H-pyrazol-5-

15 yl]methyl]hexahydro-1H-azepin-2-one.

217 E) The crude product of this Example, part D above, is reacted with trimethyloxonium tetrafluoroborate by the method of Example 3 to generate the iminoether. The iminoether is reacted with ammonium chloride by the

20 method of Example 5 to generate 5-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]-4,5-dihydro-1-methyl-1H-pyrazol-3-ol acetate, monohydrochloride.

217 F) The crude product of this Example, part E above, is heated in 2N HCl to generate the title compound.

25

Example 218

5-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]-1,2-dihydro-
30 3H-pyrazol-3-one, dihydrochloride
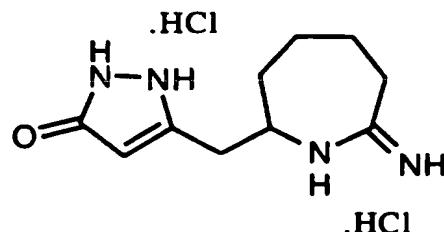
218 A) The title compound of Example 217, part B, is
reacted with hydrazine to generate 7-[(4,5-dihydro-3-
hydroxy-1H-pyrazol-5-yl)methyl]hexahydro-1H-azepin-2-one.
218 B) The crude product of this Example, part A above,
5   is reacted with acetic anhydride to generate 7-[(3-
acetyloxy-4,5-dihydro-1H-pyrazol-5-yl)methyl]hexahydro-
1H-azepin-2-one.
218 C) The crude product of this Example, part B above,
is reacted with DDQ by the method of E. W. Bousquet, J.
10 *Org. Chem.* **1975**, 40, 2208 to generate 7-[(3-acetyloxy-
1H-pyrazol-5-yl)methyl]hexahydro-1H-azepin-2-one.
218 D) The crude product of this Example, part C above,
is reacted with trimethyloxonium tetrafluoroborate by the
method of Example 3 to generate the iminoether. The
15 iminoether is reacted with ammonium chloride by the
method of Example 5 to generate 7-[(3-acetyloxy-1H-
pyrazol-5-yl)methyl]hexahydro-1H-azepin-2-imine,
monohydrochloride.
218) The crude product of this Example, part D above, is
20 heated in 2N HCl to generate the title compound.

Example 219 and Example 64

25 Isomer A: (±)(cis) 4-methyl-5-(phenylmethyl)pyrrolidin-
2-imine, monohydrochloride
Isomer B: (±)(trans) 4-methyl-5-
(phenylmethyl)pyrrolidin-2-imine, monohydrochloride
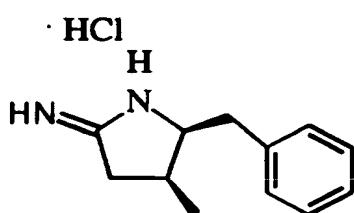
Example 219
Isomer A
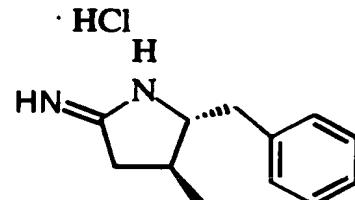
Example 64
Isomer B

Example 219 A) *trans*-b-Nitrostyrene (63.0 g, 0.42 mole) was
reacted with benzaldehyde (53.4 g, 0.5 mole) and 1,2-
diaminobenzene (54.4 g, 0.5 mole) according to the procedure
of Chikashita et. al. (*Synth. Commun.* **1985,** 15 (6), 527) to
5   yield (2-nitroethyl)benzene (60.0 g, 95%) as a yellow oil.
Example 219 B) Methyl crotonate (6.4 g, 64 mmol) was mixed
with the product of Example 219 A (9.7 g, 64 mmol),
potassium carbonate (8.9 g, 64 mmol) and Aliquat 336 (20
drops). The mixture was sonicated at room temperature.
10 When the reaction, monitored by G.C., was complete, the
mixture was acidified with HCl (1 N) and the aqueous phase
extracted with ether. The organic phase was dried (Na2SO4),
filtered and stripped of solvent under reduced pressure to
provide the crude product oil. Purification by
15 chromatography on silica gel yielded methyl b-methyl-g-
nitrobenzenepentanoate (14.7 g, 91%).
Example 219 C) The product material from Example 219 B (5.0
g, 20 mmol) in absolute MeOH was hydrogenated over RaNi at
55 °C and 60 psi for 24h. The reaction product was purified
20 by column chromatography to yield 4-methyl-5-
(phenylmethyl)pyrrolidin-2-one (2.4 g, 62%) as a mixture of
diasteromers.
Example 219 D) The products of Example 219 C (1.35 g, 7.0
mmol) were treated with trimethyloxonium tetrafluoroborate
25 (1.26 g, 8.6 mmol) in CH2Cl2 (DCM, 20 mL) by the method of
Example 3, to yield 3,4-dihydro-5-methoxy-3-methyl-2-
(phenylmethyl)-2H-pyrrole (1.0 g, 67%) as a mixture of
diastereomers.
Example 219 and Example 64) A solution of the product of
30 Example 219 D (1.0 g, 4.7 mmol) in MeOH (30 mL) was reacted
with ammonium chloride (200 mg, 3.8 mmol) by the method of
Example 5 followed by chromatography on reverse phase HPLC
to generate the cis and trans title materials 219 (300 mg)
and 64 (220 mg). The sample of trans isomer obtained by
35 this method was identical to that obtained the method of
Example 64.

DSC: 142.1 °C

Elemental analysis: $C_{12}H_{16}N_2 \cdot 1.09$ HCl (MW=228.01)

	C	H	N	Cl
Calculated:	63.21	7.55	12.29	16.95
Found:	63.53	7.56	12.11	17.29

Examples 220

Isomer A: (±)(*cis*) 5-(phenylmethyl)-4-(trifluoromethyl)pyrrolidin-2-imine, monohydrochloride

Isomer B: (±)(*trans*) 5-(phenylmethyl)-4-(trifluoromethyl)pyrrolidin-2-imine, monohydrochloride
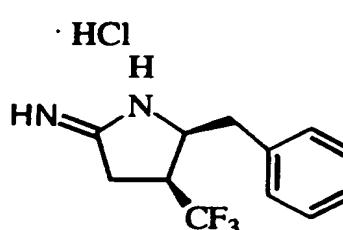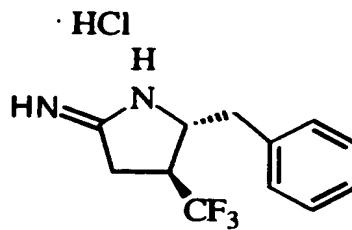
Isomer A   Isomer B

Example 220 A) Ethyl 4,4,4-trifluomethyl crotonate (5.5 g, 33 mmol) and the product of Example 219 A (5.0 g, 33 mmol) were reacted with potassium carbonate (4.6 g, 33 mmol) and Aliquat 336 (10 drops), by the method of Example 219 B. Purification by chromatography on silica gel yielded the product ethyl g-nitro-b-(trifluoromethyl)benzenepentanoate (4.4 g, 42%).

Elemental analysis: $C_{14}H_{16}NO_4F_3$ (MW=359.28)

	C	H	N
Calculated:	52.67	5.05	4.39
Found:	52.81	5.40	4.31

Example 220 B) The material 220 A (4.3 g, 13.5 mmol) in absolute MeOH was hydrogenated over RaNi at 55 °C and 60 psi for 16h. The reaction product was purified by column chromatography to yield 5-(phenylmethyl)-4-

(trifluoromethyl)pyrrolidin-2-one (2.3 g, 71%) as a mixture of diasteromers.

Example 220 C) The product material from Example 220 B (0.74 g, 3 mmol) was treated with trimethyloxonium tetrafluoroborate (0.54 g, 3.7 mmol) in DCM (20 mL) by the method of Example 3, to yield 3,4-dihydro-5-methoxy-2-(phenylmethyl)-3-(trifluoromethyl)-2H-pyrrole (0.58 g, 76%) as a mixture of diastereomers.

Example 220) A solution of the product of Example 220 C (0.6 g, 2.3 mmol) in MeOH (20 mL) was reacted with ammonium chloride (134 mg, 2.3 mmol) by the method of Example 5 followed by chromatography on reverse phase HPLC to generate the cis and trans title materials 220 Isomer A (240 mg) and 220 Isomer B (250 mg).

Example 220 Isomer A:

Elemental analysis: $C_{12}H_{13}N_2F_3 \cdot 1\ HCl \cdot 1.1\ NH_4Cl \cdot 0.67\ H_2O$ (MW=349.62)

	C	H	N	Cl
Calculated:	41.23	5.69	12.42	21.30
Found:	41.01	5.34	12.65	21.67

Example 220 Isomer B:

Elemental analysis: $C_{12}H_{13}N_2F_3 \cdot 1\ HCl \cdot 0.1\ AcOH$ (MW=284.71)

	C	H	N
Calculated:	51.47	5.10	9.84
Found:	51.87	5.20	9.59

Example 221

4,4-dimethyl-5-(phenylmethyl)pyrrolidin-2-imine, monohydrochloride
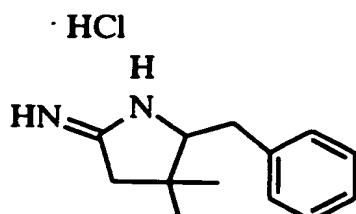
Example 221 A) Ethyl dimethyl acrylate (10.75 g, 84 mmol)
was mixed with the product of Example 219 A (12.68 g, 84
mmol), in tetra-n-butylammonium fluoride in THF (84 mL, 1 M)
and heated at 40 °C. When the reaction, monitored by G.C.,
was complete, the mixture was treated with brine (satd.) and
the aqueous phase extracted with ether. Purification by
chromatography on silica gel yielded the product ethyl b,b-
dimethyl-g-nitrobenzenepentanoate (9.04 g, 34 %).

Elemental analysis: $C_{15}H_{21}NO_4$ (MW=279.34)

	C	H	N
Calculated:	64.50	7.58	5.01
Found:	64.60	7.96	4.96

Example 221 B) The product material from Example 221 A (3.5
g, 12.5 mmol) in absolute MeOH was hydrogenated over RaNi at
55 °C and 60 psi for 6 h. The reaction product was purified
by column chromatography to yield 4,4-dimethyl-5-
(phenylmethyl)pyrrolidin-2-one (2.41 g, 95%).
Example 221 C) The product material from Example 221 B
(1.04 g, 5.1 mmol) was treated with trimethyloxonium
tetrafluoroborate (0.91 g, 6.2 mmol) in DCM (25 mL) by the
method of example 3, to yield 3,4-dihydro-5-methoxy-3,3-
dimethyl-2-(phenylmethyl)-2H-pyrrole (0.83 g, 75%).
Example 221) A solution of the product of Example 221 C
(0.8 g, 3.5 mmol) in MeOH (60 mL) was reacted with ammonium
chloride (187 mg, 3.5 mmol) by the method of Example 5
followed by chromatography on reverse phase HPLC to generate
the title material (570 mg, 68 %).

Elemental analysis: $C_{13}H_{18}N_2$ · 1.0 HCl (MW=238.76)

	C	H	N	Cl
Calculated:	65.40	8.02	11.73	14.85
Found:	65.04	7.78	11.85	14.75

Example 222

5-(phenylmethyl)pyrrolidin-2-imine, monohydrochloride

5
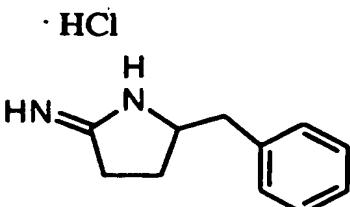
Example 222 A) Methyl acrylate (2.8 g, 33 mmol) was mixed with the product of Example 219 A (5.0 g, 33 mmol), potassium carbonate (4.6 g, 33 mmol) and Aliquat 336 (10 drops), by the method of Example 219 B. Purification by chromatography on silica gel yielded 4.0 g (55%) of methyl g-nitrobenzenepentanoate.

Elemental analysis: $C_{12}H_{16}NO_4$ · 0.05 hexane (MW=242.57)

	C	H	N
Calculated:	61.16	6.55	5.80
Found:	61.54	6.52	6.16

Example 222 B) The product material from Example 222 A (4.0 g, 18 mmol) was hydrogenated over Pd/C (4%) at 55 °C and 5 psi for 40 h. The reaction product was purified by column chromatography to yield 5-(phenylmethyl)pyrrolidin-2-one (0.6 g, 29%).

Example 222 C) The product material of Example 222 B (0.5 g, 3.1 mmol) was treated with trimethyloxonium tetrafluoroborate (0.55 g, 3.7 mmol) in DCM (25 mL) by the method of Example 3, to yield 3,4-dihydro-5-methoxy-2-(phenylmethyl)-2H-pyrrole (0.5 g, 78%).

Example 222) A solution of the title product of Example 222 C (0.5 g, 2.4 mmol) in MeOH (20 mL) was reacted with ammonium chloride (0.14 g, 2.7 mmol) by the method of Example 5. The crude product residue after removal of solvent was subjected to reverse phase HPLC to generate the title material (0.31 g, 55%).

Elemental analysis: $C_{11}H_{14}N_2 \cdot 1\ HCl \cdot 0.35\ NH_4Cl \cdot 0.25\ H_2O$
(MW=233.93)

	C	H	N	Cl
Calculated:	56.48	7.28	14.07	20.46
Found:	56.43	7.48	14.38	20.83

Examples 223

Isomer A: (±)(cis) 5-[(1,3-dioxolan-2-yl)methyl]-4-
(trifluoromethyl)pyrrolidin-2-imine, monohydrochloride
Isomer B: (±)(trans) 5-[(1,3-dioxolan-2-yl)methyl]-4-
(trifluoromethyl)pyrrolidin-2-imine, monohydrochloride
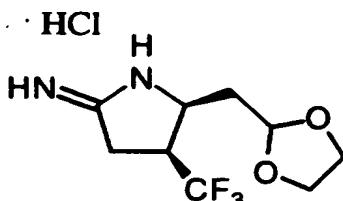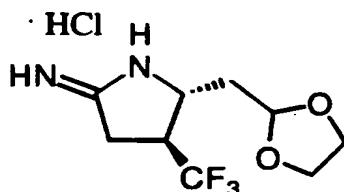
Isomer A   Isomer B

Example 223 A)   Ethyl 4,4,4-trifluomethyl crotonate (10
mmol) and 2-(2-nitroethyl)-1,3-dioxolane (12 mmol) are
reacted with potassium carbonate (5 mmol) and Aliquat 336 (3
drops), by the method of Example 219 B.   Purification by
chromatography on silica gel yields ethyl g-nitro-b-
(trifluoromethyl)-1,3-dioxolane-2-pentanoate.

Example 223 B)   The product material from Example 223 A in
MeOH is hydrogenated over RaNi at 55 °C and 60 psi for 6 h.
The reaction product is purified by column chromatography to
yield 5-[(1,3-dioxolan-2-yl)methyl]-4-
(trifluoromethyl)pyrrolidin-2-one as a mixture of
diasteromers.

Example 223C)   The product material from Example 223 B is
treated with trimethyloxonium tetrafluoroborate in DCM by
the method of Example 3 to yield 2-[(1,3-dioxolan-2-
yl)methyl]-3,4-dihydro-5-methoxy-3-(trifluoromethyl)-2H-
pyrrole as a mixture of diastereomers.

Example 223)   A solution of the title products of Example
223 C in MeOH are reacted with ammonium chloride by the
method of Example 5 followed by chromatography on reverse
phase HPLC to generate the cis and trans title materials 223
5   Isomer A and 223 Isomer B.

Examples 224

10   Isomer A: (±)(trans) 2-[2-hydroxy-3-[5-imino-3-
     (trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
     carboxylic acid, monohydrochloride
     Isomer B: (±)(cis) 2-[2-hydroxy-3-[5-imino-3-
     (trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
15   carboxylic acid, monohydrochloride
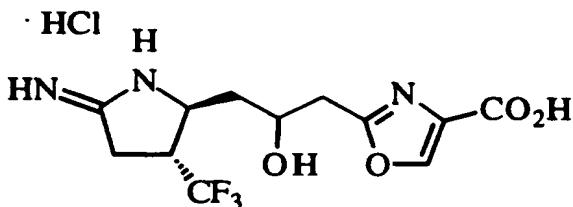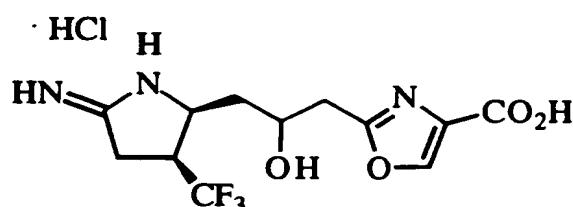
20   Isomer A   Isomer B

Example 224 A)   The product of Example 223 B in MeOH is
treated with HCl (1N) to yield 5-oxo-3-
(trifluoromethyl)pyrrolidine-2-acetaldehyde which is used
25   directly in the next step.
Example 224 B)   As described by Helquist et al. in J.
Org. Chem., 1992, 57, 4799-4802, to a stirring
suspension of Zn (7.5 mg-atm) and the product of 224 A
(5.5 mmol) in 10 mL of THF at 0 °C is added dropwise
30   ethyl 2-bromomethyloxazole-4-carboxylate (U.S. pat.
5,395,932) (5.0 mmol) in 10 mL of THF. After stirring
for 2 h, the reaction is quenched with saturated NH4Cl
and extracted with Et2O. The organic phase is dried over
MgSO4, concentrated under vacuum, and purified by column
35   chromatography to give ethyl 2-[2-hydroxy-3-[5-oxo-3-

(trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
carboxylate.

Example 224 C)   To a stirring solution of 224 B (5 mmol)
in 10 mL of MeOH is added 10 mL of 1N NaOH. After 2 h,
5   the reaction mixture is adjusted to pH 3 with 1M KHSO4.
The reaction mixture is extracted 3x 50 mL of EtOAc. The
combined organic layers are dried over Na2SO4 anhydrous,
filtered, and stripped to give 2-[2-hydroxy-3-[5-oxo-3-
(trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
10 carboxylic acid.

Example 224 D)   To a stirring solution of the product of
Example 224 C (5 mmol) and imidazole (6 mmol) in 10 mL of
DMF is added t-butyldimethylsilyl chloride (12 mmol).
After 16 h, the solvent is removed under high vacuum and
15 the residue is purified by column chromatography to
provide (1,1-dimethylethyl)dimethylsilyl 2-[2-[(1,1-
dimethylethyl)dimethylsilyloxy]-3-[5-oxo-3-
(trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
carboxylate.

20 Example 224 E)   The product of Example 224 C is treated with
trimethyloxonium tetrafluoroborate in DCM by the method of
Example 3 to yield (1,1-dimethylethyl)dimethylsilyl 2-[3-
[3,4-dihydro-5-methoxy-3-(trifluoromethyl)-2H-pyrrol-2-yl]-
2-[(1,1-dimethylethyl)dimethylsiloxy]propyl]oxazole-4-
25 carboxylate as a mixture of diastereomers.

Example 224)   A solution of the title products of Example
224 D in MeOH are reacted with ammonium chloride by the
method of Example 5. The material is dissolved in HCl (2N)
and refluxed for 2h. The crude product residue after
30 removal of solvent was subjected to reverse phase HPLC to
generate both the cis and trans title materials 224 Isomer A
and 224 Isomer B.

Example 225

Isomer A: (±)ethyl (*trans*)   2-[3-[5-imino-3-
(trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
carboxylate, monohydrochloride
Isomer B: (±)ethyl (*cis*)   2-[3-[5-imino-3-
(trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
carboxylate, monohydrochloride

Isomer A   Isomer B
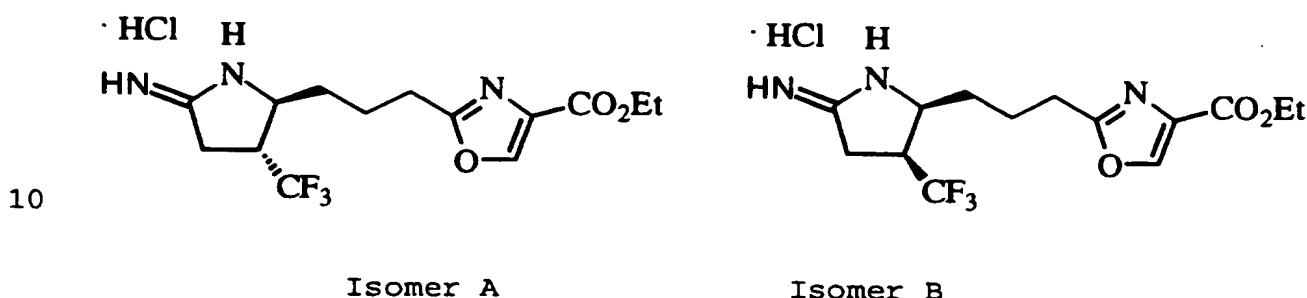
Example 225A)   To a stirring solution of the product of
Example 224 B (5 mmol) in 10 mL of 10 % TFA/DCM is added
Et$_3$SiH (7.5 mmol).   After stirring for 30 min, the
solvent is removed under vacuum and the residue is
purified by column chromatography to provide ethyl 2-[3-
[5-oxo-3-(trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-
4-carboxylate.
Example 225 B)   The product material from Example 225 A is
treated with trimethyloxonium tetrafluoroborate in DCM by
the method of Example 3, to yield ethyl 2-[3-[3,4-dihydro-5-
methoxy-3-(trifluoromethyl)-2H-pyrrol-2-yl]propyl]oxazole-4-
carboxylate as a mixture of diastereomers.
Example 225)   A solution of the product of Example 225 B in
MeOH is reacted with ammonium chloride by the method of
Example 5.   The crude product residue after removal of
solvent was subjected to reverse phase HPLC to generate both
the cis and trans title materials 225 Isomer A and 225
Isomer B.

Example 226

Isomer A: (±) (*trans*) 2-[3-[5-imino-3-
(trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
carboxylic acid, monohydrochloride

Isomer B: (±) (*cis*) 2-[3-[5-imino-3-
(trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
carboxylic acid, monohydrochloride

Isomer A   Isomer B
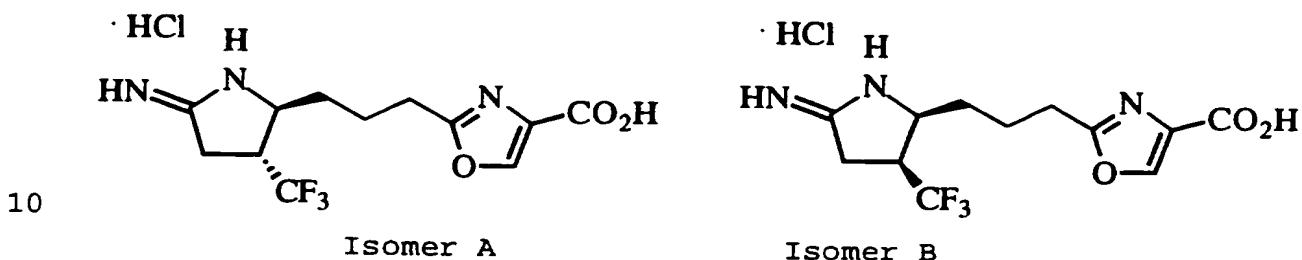
A solution of the crude title product mixture of Example 225
in HCl (2N) is reacted by the method of Example 224 E. The
crude product residue after removal of solvent was subjected
to reverse phase HPLC to generate the title material to
generate both the cis and trans title materials 226 Isomer A
and 226 Isomer B.

Examples 227

Isomer A: (±) (*cis*) 5-[(4-methoxyphenyl)methyl]-3-
methylpyrrolidin-2-imine, monohydrochloride

Isomer B: (±) (*trans*) 5-[(4-methoxyphenyl)methyl]-3-
methylpyrrolidin-2-imine, monohydrochloride

Isomer A   Isomer B
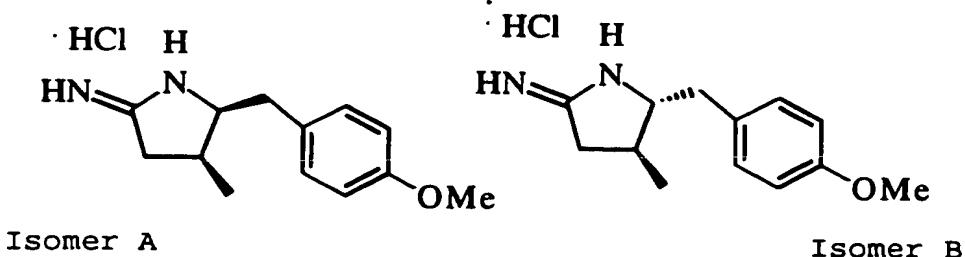
Example 227 A)   4-Methoxy-β-nitrostyrene (25.0 g, 0.15 mole)
was reacted with benzaldehyde (19.1 g, 0.18 mole) and 1,2-

diaminobenzene (19.8 g, 0.18 mole) according to the procedure of Chikashita et. al. (*Synth. Commun.* **1985**, 15 (6), 527) to yield methoxy-4-(2-nitroethyl)benzene (25.0 g, 93%) as a yellow oil.

5 Example 227 B) Methyl crotonate (6.1 g, 61 mmol) was mixed with the product of Example 227 A (10 g, 61 mmol), potassium carbonate (8.4 g, 61 mmol) and Aliquat 336 (10 drops). The mixture was sonicated at room temperature. When the reaction, monitored by G.C., was complete the mixture was

10 acidified with HCl (1 N) and the aqueous phase extracted with ether. Purification by chromatography on silica gel gave methyl 4-methoxy-b-methyl-g-nitrobenzenepentanoate (6.7 g, 39%).

Example 227 C) The product of Example 227 B (6.7 g, 24

15 mmol) in MeOH was hydrogenated over RaNi at 55 °C and 60 psi for 16 h. The reaction product was purified by column chromatography to yield 5-[(4-methoxyphenyl)methyl]-4-methylpyrrolidin-2-one (3.3 g, 67%) as a mixture of diasteromers.

20 Example 227 D) The product from Example 227 C (1.4 g, 6.6 mmol) was treated with trimethyloxonium tetrafluoroborate (1.2 g, 7.5 mmol) in DCM by the method of Example 3, to yield 3,4-dihydro-5-methoxy-2-[(4-methoxyphenyl)methyl]-3-methyl-2H-pyrrole (1.4 g, 95%) as a mixture of

25 diastereomers.
Example 227) A solution of the title product of Example 227 D in MeOH is reacted with ammonium chloride by the method of Example 5. The crude product residue after removal of solvent was subjected to reverse phase HPLC to

30 generate the cis and trans title materials 227 Isomer A and 227 Isomer B.

Example 228

35

hexahydro-3-[[(methoxyphenyl)methyl]thio]-2H-azepin-2-imine, trifluoroacetate salt
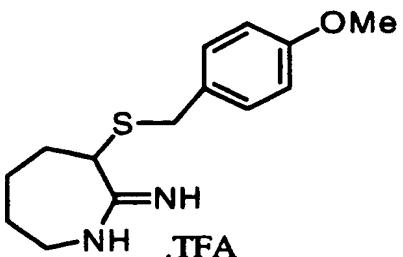
Example 228 A)   To a solution of 10 g (0.088 mol) of
caprolactam in 200 mL of anhydrous THF was added 38.2 g
5   (0.177 mol) of Boc-anhydride and 0.2 g DMAP. This
mixture was stirred at reflux for 4 days, allowed to cool
to 25 °C, diluted with EtOAc, washed with aqueous sodium
bicarbonate, dried (MgSO$_4$), filtered and concentrated to
afford the N-Boc-caprolactam as a yellow oil.
10   Chromatography (silica gel, ethyl acetate/hexanes)
afforded 14 g of the Boc-protected caprolactam as a pale
yellow oil.
Example 228 B)   To a solution of 1 g (0.0047 mol) of this
Boc-caprolactam product of Example 228 A in 10 mL of
15   anhydrous THF at -78 °C was added 0.005 mol of LiHMDS.
After stirring for 30 minutes, 1.2 g (0.005 mol) of
hexachloroethane in 5 ml of anhydrous THF was added. The
mixture was allowed to warm to 0 °C and was quenched with
dilute HCl. The mixture was extracted with EtOAc and the
20   organic layer was washed with 5% HCl, dried (MgSO$_4$),
filtered and concentrated to afford a yellow oil. The
residue oil was dissolved in 40 mL of 1,4-dioxane (satd.
with anhydrous HCl), stirred for 40 minutes, concentrated
to afford 0.9 g of 3-chlorocaprolactam as an off-white
25   solid.
Example 228 C)   A solution of 0.45 g (0.003 mol) of the
3-chlorocaprolactam product of Example 228 B in 5 mL of
methylene chloride was treated with 0.5 g (0.0033 mol)
of Me$_3$O$^+$BF$_4$$^-$. This mixture was stirred for 18 hours at 25
30   °C. The solution was diluted with EtOAc before the
organic fraction was washed with aqueous sodium
bicarbonate, dried (MgSO$_4$), filtered and concentrated to
afford 0.3 g of the iminoether as a yellow oil. This

iminoether was dissolved in 5 mL of methanol and 0.1 g
(0.0019 mol) of ammonium chloride was added. The mixture
was stirred at 60 °C for 3 days. The solvent was removed
in vacuo and the residue, dissolved in water, was washed
5   with EtOAc. Chromatography (C-18, acetonitrile/ water)
followed by lyophilization afforded 2-imino, 3-
chlorohexamethyleneimine as a white solid.
Example 228) To a solution of 4-methoxybenzylmercaptan
in 50 mL of anhydrous THF was added 0.55 g (0.0135 mol)
10 of sodium hydride. After stirring at 25 °C for fifteen
minutes, 1.6 g (0.006 mol) of the 2-imino, 3-
chlorohexamethyleneimine product of Example 228 C was
added. This mixture was stirred at reflux for 6 hours
and then at 25 °C for 3 days. The reaction mixture was
15 diluted with dilute HCl and concentrated to afford a
sticky off-white solid. The residue was dissolved in
water, washed with EtOAc, and chromatographed (C-18,
acetonitrile/water) top afforded 1.6 g of the title
product as a yellow oil.
20

Mass spectral analysis for $C_{13}H_{18}N_2S_1$: $M^+H = 265$.

^1H NMR(D_2O): δ 1.2-2.0(m, 6H), 3.2 (m, 1H), 3.5 (m, 1H),
3.65 (bs, 5H), 3.7 (d, 2H), 6.8 (d, 2H), 7.15 (d, 2H).
25

Example 229

2-[2-(2-iminohexahydro-1H-azepin-3-yl)ethyl-1-
30 methylpyridinium chloride, monohydrochloride
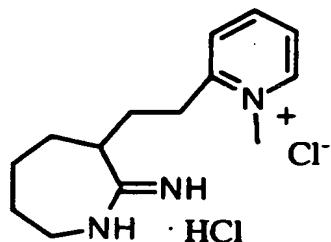
The title material was prepared by the method of Example
291 using hexahydro-3-[2-(2-pyridyl)ethyl]-1H-azepin-2-
one material prepared in Example 290).

5   Mass spectral analysis for $C_{14}H_{22}N_3$: M^+H = 232.

^1H NMR (D_2O): δ 8.60 (d, J = 7 Hz, 1H); 8.35 (t, J = 7
Hz, 1H); 7.85 (d, J = 7 Hz, 1H); 7.75 (t, J = 7 Hz, 1H);
4.2 (s, 3H); 3.42 - 3.30 (m, 2H); 3.22 - 3.00 (m, 2H);
10   3.00 - 2.80 (m, 1H); 2.30 - 2.00 (m, 2H); 1.90 - 1.50 (m,
6H).

Example 230

15

hexahydro-3-[2-(1-methylpiperidin-2-yl)ethyl]-2H-azepin-
2-imine, dihydrochloride

20
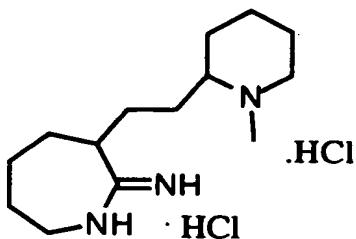
The title material was prepared by the method of Example
292 from the product of Example 229.

Mass spectral analysis for $C_{14}H_{27}N_3$: M^+H = 238.
25

^1H NMR (D_2O): δ 3.40 - 3.20 (m, 3H); 3.20 - 2.05 (m, 3H);
2.80 - 2.60 (m, 4H); 1.90 - 1.20 (m, 15H).

30   Example 231

ethyl 5-[(hexahydro-2-imino-1H-azepin-3-yl)methyl]-4,5-
dihydroisoxazole-3-carboxylate, trifluoroacetate salt
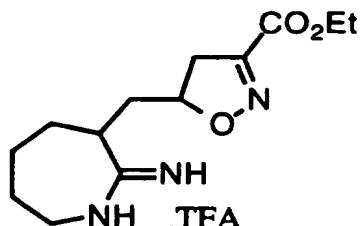
Example 231 A)   The Isomer A title product of Example 18
(3-allylcaprolactam, 5 g, 0.033 mol) was reacted with 10
5   g (0.066 mol) of ethyl chlorooximidoacetate in 500 mL of
toluene. This mixture was stirred at reflux for 18
hours. The reaction mixture was allowed to cool and then
concentrated to afford a brown oil. Chromatography of
this oil (silica gel, EtOAc) afforded 7 g of 3-[[4,5-
10   dihydro-3-(ethoxycarbonyl)isoxazol-5-yl]methyl]
hexahydro-1H-azepin-2-one as a yellow oil.

Mass spectral analysis for $C_{13}H_{20}N_2O_4$: $M^+H = 269$.

15   Example 231)   To a magnetically stirred slurry of 3 g
(0.021 mol) of $Me_3O^+BF_4^-$ and 60 mL of CH_2Cl_2 under
nitrogen (N_2) was added 5 g (0.019 mol) of the 3-[[4,5-
dihydro-3-(ethoxycarbonyl)isoxazol-5-yl]methyl]
hexahydro-1H-azepin-2-one product of Example 231 A. This
20   mixture was stirred at room temperature for 18 hours
before it was diluted with 30 mL of EtOAc and partitioned
between the organic layer and 40 mL of saturated $NaHCO_3$.
The organic phase was separated, dried ($MgSO_4$), filtered,
and concentrated under reduced pressure to provide 5.3 g
25   of the iminoether as a red oil. This iminoether and 1.1
g (0.021 mol) of ammonium chloride (NH_4Cl) were refluxed
in 25 mL of methanol (MeOH) under a nitrogen atmosphere
for 18 hours. After cooling the reaction to room
temperature, it was concentrated to give a dark residue
30   which was filtered and partitioned between water and
EtOAc. The organic and aqueous phases were separated and
the aqueous phase was washed with a 15 mL portion of
EtOAc. Chromatography of the aqueous layer (C-18,

acetonitrile/water) afforded 2.5 g of the title product
as a red oil.

Mass spectral analysis for $C_{13}H_{21}N_3O_3$: M^+H = 268

5

^{1}H NMR(D_2O): δ 1.2 (t, 3H), 1.4-2.2 (m, 8H), 2.9 (m, 2H),
3.35 (m, 3H), 4.2 (q, 2H), 4.9 (m, 1H).

10   Example 232

cyclohexyl hexahydro-7-iminoazepine-2-carboxylate,
monohydrochloride
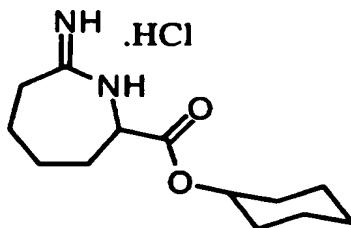
15

A solution of 0.1 g of the 2-imino, 3-
carbomethoxyhexamethyleneimine product of Example 233d in
5 mL of cyclohexanol was treated with 5 drops of acetyl
20   chloride and stirred at reflux for eighteen hours. After
cooling the reaction to room temperature, it was
concentrated in vacuo to afford a sticky oil.
Lyophilization afforded the title compound as an off-
white solid.
25

Mass spectral analysis for $C_{13}H_{22}N_2O_2$: M^+H = 239.

^{1}H NMR(D_2O): δ 1.1-1.85 (m, 15H), 2.05 (m, 1H), 2.55 (m,
2H), 4.35 (dd, 1H), 4.75 (h, 1H).

30

Example 233

phenylmethyl hexahydro-7-iminoazepine-2-carboxylate,
monohydrochloride
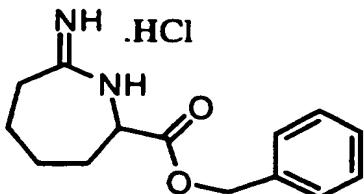
5

Example 233 A) Anhydrous HCl was bubbled into a mixture
of 25 g (0.14 mol) of 2-aminopimellic acid in 500 mL of
methanol until the solid was dissolved. After standing
for 18 hours, the reaction was concentrated to afford

10   33.5 g (100% yield) of the bis-methyl ester salt as a
white solid.
Example 233 B) The HCl salt product of Example 233 A was
neutralized by the addition of a small amount of water
containing 1 equivalent of sodium bicarbonate. This

15   solution was extracted with EtOAc, dried (MgSO$_4$),
filtered and concentrated to afford 22 g of the free
base.
Example 233 C) A solution of 17 g (0.084 mol) of the
free base product of Example 233 B in 900 mL of p-cymene

20   was stirred at reflux for two days. The solvent was
removed in vacuo and the residue recrystallized from
cyclohexane to afford 12.2 g (85% yield) of 7-
(methoxycarbonyl)caprolactam as an off-white solid.
Example 233 D) A solution of 0.3 g (0.0018 mol) of the

25   lactam product of Example 233 C in 10 mL of methylene
chloride was treated with 0.3 g (0.002 mol) of Me$_3$O$^+$BF$_4^-$.
This mixture was stirred for 18 hours at 25 °C. The
solution was diluted with EtOAc, washed with aqueous
sodium bicarbonate, dried (MgSO$_4$), filtered and

30   concentrated to afford 0.25 g of the iminoether as a
yellow oil. The iminoether was dissolved in 10 mL of
methanol and 0.08 g (0.0014 mol) of ammonium chloride was
added to the solution. This mixture was stirred at 60 °C
for 6 hours. The solvent was removed in vacuo and the

35   residue dissolved in water was washed with EtOAc, and

lyophilized to afford 2-imino, 3-
carbomethoxyhexamethyleneimine as an off-white foam.
Example 233)   A solution of 0.1 g of the 2-imino, 3-
carbomethoxyhexamethyleneimine product of Example 233 D
in 5 mL of benzyl alcohol was treated with 5 drops of
acetyl chloride and stirred at reflux for eighteen hours.
Removed heat and concentrated in vacuo to afford a sticky
oil. Lyophilization afforded the title compound as an
off-white solid.

^{1}H NMR(D$_2$O): δ 1.2-1.95 (m, 5H), 2.05 (m, 1H), 2.5 (m,
2H), 4.4 (dd, 1H), 5.2 (q, 2H), 7.3 (s, 5H)

Mass spectral analysis for C$_{14}$H$_{18}$N$_2$O$_2$: M$^+$H = 247

Example 234

hexahydro-7-[3-(phenylmethoxy)propyl]-2H-azepin-2-imine,
trifluoroacetate salt
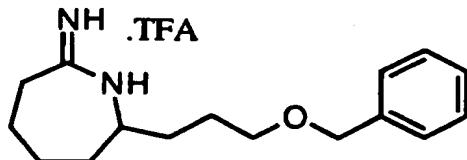
Example 234 A)   To a mechanically stirred mixture of
KOt-Bu (10.1 g, 104 mmol) in benzene (100 mL) cooled to 0
°C under nitrogen was added cyclohexanone (7.4 g, 83
mmol) dropwise over 20 min. Ten minutes after the
addition was complete, benzyl 3-bromo-propyl ether (20 g,
87 mmol) was added over a twenty minute period. The
reaction mixture was warmed to room temperature, refluxed
for seven hours, stirred at room temperature for eighteen
hours, and diluted with 0.5 N potassium hydrogen sulfate
(200 mL). The reaction mixture was further diluted with
Et$_2$O, 0.5 N potassium hydrogen sulfate, and water, until
two phases formed. The organic phase was washed with

water, brine, dried over sodium sulfate, filtered, and
the solvent removed under reduced pressure to give 19.2 g
of the 2-(3-benzyloxypropyl)-cyclohexan-1-one.

5   Mass spectral analysis for $C_{16}H_{22}O_2$: M^+H = 247.

^1H NMR ($CDCl_3$): δ 0.8-2.5 (m, 13H), 3.40-3.45 (m, 2H),
4.5 (s, 2H), 7.2-7.4 (m, 5H).

10   Example 234 B)   To the product from Example 234 A (4.9 g,
20 mmol) in 40 mL EtOH and 30 mL water was added
hydroxylamine hydrochloride (2.1 g, 30 mmol) and sodium
acetate (3.3 g, 40 mmol). The mixture was refluxed for 4
hours, followed by stirring for 18 hours at room
15   temperature. The EtOH was evaporated in vacuo and the
solution was diluted with 100 mL water and extracted with
EtOAc. The organic phase was washed with brine, dried
over $MgSO_4$ and concentrated in vacuo, yielding 5.7 g of
the 2-(3-benzyloxypropyl)-cyclohexanone oxime as an oil.
20   Example 234 C)   The 2-(3-benzyloxypropyl)-cyclohexanone
oxime product of Example 234 B was dissolved in 20 mL
acetone and was reacted with benzenesulfonyl chloride
(3.5 g, 20 mmol) at 0 °C in the presence of 20 mL 1 N
NaOH. The mixture was stirred for 18 h at room
25   temperature and the acetone was evaporated, diluted with
100 mL water, and extracted with EtOAc. The organic
phase was washed with brine and concentrated in vacuo to
yield 4.3 g of a mixture of the 3 and 7 isomers of
benzyloxypropylcaprolactam. The crude material was
30   purified by HPLC chromatography on silica gel using 30%
acetone in hexane to obtain 1.3 g of the 7-
(benzyloxypropyl)caprolactam as oil.

Mass spectral analysis for $C_{16}H_{23}N_1O_2$: M^+H = 262.
35

Example 234 D)   To the product from Example 234 C (1.3 g,
5.0 mmol) dissolved in 25 mL CH_2Cl_2 was added $Me_3O^+BF_4^-$
(0.8 g, 1.1 equiv.), and the mixture stirred for 16

hours. The solvent was removed under reduced pressure
and the resulting oil was dissolved in 50 mL MeOH. This
solution was saturated with ammonia gas at 0 °C for 20
minutes. The flask was stoppered and the reaction was
5   stirred at room temperature for 16 hours. The reaction
was concentrated by evaporation and the residue was
subjected by reverse phase HPLC (C-18), to give 0.87 g of
the title product as a white powder.

10   Mass spectral analysis for $C_{16}H_{24}N_2O$: $M^+H = 261$.

^1H NMR ($CDCl_3$): δ 1.37-1.55 (m, 3H), 1.65-1.83 (m, 5H),
1.90-2.04 (m, 2H), 2.40-2.63 (m, 2H), 3.34-3.43 (m, 1H),
3.43-3.52 (m, 2H), 4.49 (s, 2H), 7.26-7.34 (m, 5H).
15

Example 235

N-[2-(hexahydro-7-imino-1H-azepin-2-
20   yl)ethyl]benzenimidamide, bis(trifluoroacetate) salt
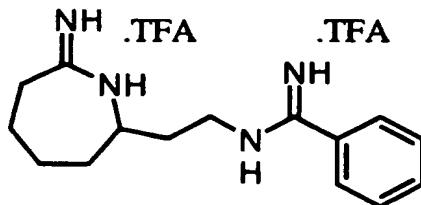
Example 235 A)   A sample of 2-nitroethanol (10 g, 110 mmol)
25   was added over a period of 30 minutes to a mixture of
sodium acetate (2.5 g) and acetic anhydride (13 g, 127
mmol) cooled in an ice bath and maintained under a N_2
atmosphere. After 1 hour of stirring, the ice bath was
removed and the mixture was stirred for 12 hours at room
30   temperature. The reaction was diluted with 200 mL of water
and extracted with 3x100 mL of EtOAc. The combined
extracts were washed with brine, dried ($MgSO_4$) and
concentrated of all solvent in vacuo to afford the 2-nitro
ethylacetate as a clear oil.

Example 235 B)   The 2-nitro ethylacetate product of Example
235 A (13.3 g, 100 mmol) was dissolved in 15 mL
acetonitrile (AcN) which was added to a solution of 1-
morpholino cyclohexene (18.4 g, 110 mmol) in 30 mL of AcN
5   at -20 °C under N_2. After the addition was complete,
stirring was continued for 16 hours at room temperature.
After 40 mL of 1 N HCl was added to the solution, stirring
was continued for 4 more hours. The mixture was diluted
with 100 mL water and extracted with 3x100 mL EtOAc. The
10   combined organic phase was washed with brine, dried (MgSO$_4$)
and evaporated in vacuo to yield 14.5 g 2-(2-nitro
ethyl)cyclohexanone as dark oil (85% yield).

Mass spectral analysis for $C_8H_{13}NO_3$: M^+H = 172 and M^+Li =
15   178.

Example 235 C)   The 2-(2-nitroethyl)cyclohexanone product
of Example 235 B (3.42 g, 20 mmol) in 25 mL formic acid was
refluxed for 30 minutes in the presence of H_2N-OSO$_3H$ (2.48
20   g, 22 mmol). The formic acid was removed in vacuo. The
residual oil was dissolved in a mixture of water (40 mL)
and AcN (10 mL) and the isomers were separated on
preparative HPLC using AcN/H$_2$O (0.05% TFA) gradient (10-25
% AcN in 30 minutes) to yield 7-(2-nitroethyl)caprolactam:
25   1.95 g (52% yield) and 3-(2 nitroethyl)caprolactam: 0.55 g
(15% yield).

Mass spectral analysis for $C_8H_{14}N_2O_3$: M^+H = 187.

30   Example 235 D)   The 7-(2-nitroethyl)caprolactam product of
Example 235 C (2 g, 10.7 mmol) was dissolved in 30 mL
CH$_2$Cl$_2$ and reacted with Me$_3$O$^+$BF$_4^-$ (2.2 g, 15 mmol) for 16
hours. The solvent was evaporated and the residue was
dissolved in 30 mL MeOH. This solution was saturated with
35   NH$_3$ at 0 °C for 15 minutes and the mixture was stirred for
12 hours at room temperature. All solvent was removed in
vacuo and the product was isolated on preparative HPLC
using AcN/H$_2$O (0.05% TFA) gradient (0-25% AcN in 30

minutes) affording 1.85 g (93% yield) of 2-imino,7-(nitroethyl)hexamethyleneimine as a white solid.

Mass spectral analysis for $C_8H_{15}N_3O_2$: $M^+H = 186$.

^1H NMR (D_2O): δ 4.60-4.45 (t, J=7Hz, 2H); 3.70-3.55 (m, 1H); 2.70-2.40 (m, 2H); 2.30-2.15 (m, 2H); 1.90-1.25 (m, 6H)

Example 235 E) The product of Example 235 D (420 mg, 2.2 mmol) was dissolved in 30 mL EtOH (1 % HCl) and hydrogenated at 55 psi for 12 hours in the presence of 0.5 g Pd/carbon. After the catalyst was filtered off and all solvent was removed in vacuo, the residue was purified on preparative HPLC using H_2O as solvent, yielding 210 mg (62% yield) of 2-imino,7-(aminoethyl)hexamethyleneimine as a clear glassy material.

Mass spectral analysis for $C_8H_{17}N_3$: $M^+H = 156$.

^1H NMR (D_2O): δ 3.70-3.55 (m,1H); 3.05 2.90 (m,2H); 2.70-2.40 (m,2H); 2.00-1.25 (m,8H).

Example 235) The product of Example 235 E (383 mg; 1 mmol) was reacted with methylbenzimidate (343 mg; 2 mmol) in 5 mL DMF in the presence of DIPEA (0.35 mL; 2 mmol). Purification afforded 160 mg (33% yield) of the title product as a white solid.

Mass spectral analysis for $C_{15}H_{22}N_4$: $M^+H = 259$.

^1H NMR (D_2O): δ 7.65-7.40 (m,5H); 3.70-3.60 (m,1H); 3.50-3.40 (m,2H); 2.70-2.40 (m,2H); 2.05-1.30 (m,8H).

Example 236

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-3,4,5,6-
tetrahydro-2H-azepin-7-amine, bis(trifluoroacetate) salt

5
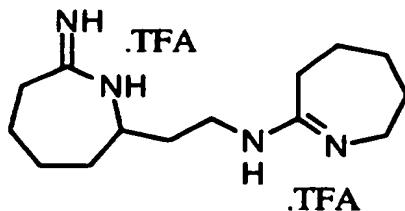
The product of Example 235 E (383 mg; 1 mmol) was reacted
with 1-aza-2-methoxy-1-cycloheptene (254 mg; 1 mmol) in 5
mL of MeOH for 16 hours at room temperature. The MeOH was
evaporated and the residue was purified on preparative
10   HPLC using AcN/H_2O gradient (0-30 % AcN in 30 minutes),

afford 470 mg (98% yield) of the title product as an
oil.

Mass spectral analysis for $C_{14}H_{26}N_4$: M^+H = 251.

15

Example 237

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-2,3,4,5-
20   tetrahydropyridin-6-amine, bis(trifluoroacetate) salt
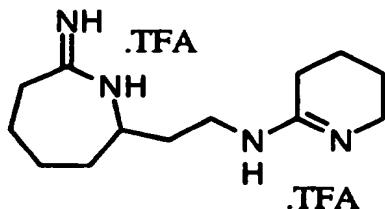
The product of Example 235 E (328 mg; 0.85 mmol) was
25   refluxed with 1-aza-2-methyl-thio-1-cyclohexene
hydroiodide (211 mg; 1 mmol) in 20 mL MeOH in the
presence of DIPEA (0.35 mL; 2 mmol) for 1 hour. The
mixture was diluted with 50 mL of H_2O and purified as
described in Example 235 affording 260 mg (88% yield) of
30   the title product as a hygroscopic material.

Mass spectral analysis for $C_{13}H_{24}N_4$: $M^+H = 237$.

Example 238

5

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-3,4-dihydro-2H-pyrrol-5-amine, bis(trifluoroacetate) salt

10
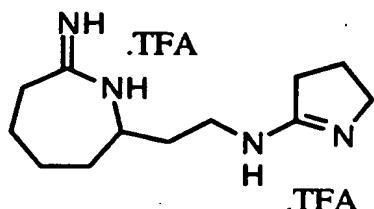
The product of Example 235 E (383 mg; 1 mmol) was reacted with 2-methoxypyrrolidine (198 mg; 2 mmol) in 20 mL MeOH for 16 hours and the product was isolated as described in Example 235 to afford 310 mg (69% yield) of the title

15   product as a white solid.

Mass spectral analysis for $C_{12}H_{22}N_4$: $M^+H = 223$.

20   Example 239

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]benzenesulfonamide, trifluoroacetate salt

25
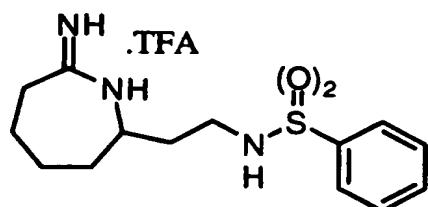
To the product of Example 235 E (0.11 g, 0.6 mmol) in 5 mL DMF was added benzenesulfonyl-chloride (0.12 g, 1.1 equiv), and the reaction mixture was maintained at

30   neutral pH by the dropwise addition of N-methylmorpholine. The reaction was quenched after 30

minutes by the addition of 1 mL water. The solvent was
removed under reduced pressure and title product was
isolated by reverse phase HPLC (C-18) to give 0.046 g of
the title material as a white powder.

5

Mass spectral analysis for $C_{14}H_{21}N_3O_2S$: M^+H = 296.

^1H NMR (D_2O): δ 1.13-1.52 (m, 3H), 1.53-1.69 (m, 3H),
1.73-1.77 (m, 2H), 2.30-2.46 (m, 2H), 2.82-2.99 (m, 2H),
10   3.37-4.51 (m, 1H), 7.48-7.61 (m, 3H), 7.74-7.78 (m, 2H).

Example 240

15   N-[2-(hexahydro-7-imino-1H-azepin-2-
yl)ethyl]benzenemethanesulfonamide, trifluoroacetate
salt
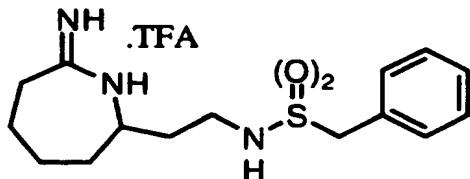
20

To the product of Example 235 E (0.27 g, 0.7 mmol) in 5
mL DMF was added α-toluenesulfonyl chloride (0.15 g, 1.1
equiv), and the resulting solution was adjusted to pH 7
with 20 drops of N-methylmorpholine and stirred for 3
25   hours. The solvent was removed under reduced pressure
and the crude residue subjected to reverse phase HPLC (C-
18) to give 0.015 g of the title product as a glassy
solid.

30   Mass spectral analysis for $C_{15}H_{23}N_3O_2S$: M^+H = 310.

^1H NMR (DMSO-d_6): δ 1.29-1.92 (m, 8H), 2.55-2.67 (m, 2H),
2.95-3.04 (m, 2H), 3.56-3.64 (m, 1H), 4.34 (s, 2H), 7.13-
7.20 (m, 1H), 7.33-7.39 (m, 5H).

35

Example 241

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]morpholin-
4-amine, bis(trifluoroacetate) salt
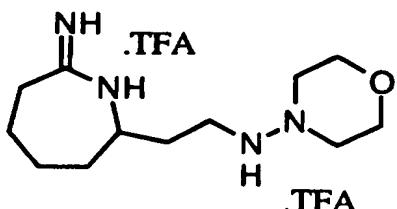
Example 241 A)   To a mechanically stirred mixture of KOt-Bu
(87 g, 0.9 mol) in benzene (700 mL) cooled to 0 °C under an
N_2 atmosphere was added cyclohexanone (67 g, 0.75 mol)
dropwise over 15 minutes. Ten minutes after the addition
was complete, bromoethyl methylether (90 g, 0.78 mol) was
added dropwise over 20 minutes. The reaction mixture was
warmed to room temperature, refluxed for 7 hours, stirred
at room temperature for 18 hours, and diluted with 0.5 N
potassium hydrogen sulfate (300 mL). The mixture was
further diluted with Et_2O (600 mL), 0.5 N potassium
hydrogen sulfate (200 mL), and water (200 mL) before the
organic phase was separated. The organic layer was washed
with water (200 mL) and brine (200 mL), dried (Na_2SO_4),
filtered, and concentrated under reduced pressure. The
crude product was distilled to afford 41 g (25% yield) of
2-(2-methoxyethyl)cyclohexanone.

Mass spectral analysis for $C_9H_{16}O_2$: M^+H = 157.

^1H NMR ($CDCl_3$): δ 3.35 (m, 2H), 3.25 (S, 3H), 2.45 (m, 1H),
2.20-2.35 (m, 2H), 1.30-2.15 (m, 8H).

Example 241 B)   The title material of Example 241 A (10 g,
64 mmol) was combined with hydroxylamine hydrochloride (8.9
g, 128 mmol) and sodium acetate (13 g, 160 mmol) in a
mixture of EtOH and water. This mixture was refluxed for 4
hours under an N_2 atmosphere. After the reaction was

cooled to room temperature and stirred for an additional 18 hours, solvent was removed under reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with 100 mL of saturated sodium

5   chloride, dried over sodium sulfate and concentrated of all solvent under reduced pressure. This provided 10.2 g (94% yield) of 2-(2-methoxyethyl)cyclohexanone oxime.

Mass spectral analysis for $C_9H_{17}N_1O_2$: $M^+H = 172$.

10

Example 241 C)   To a 250 mL round-bottomed flask was added (10 g, 71 mmol) of the oxime product of Example 241 B, 60 mL of acetone and 78 mL of 1 N NaOH. This mixture was cooled to 0 °C and benzenesulfonyl chloride (10.5 g, 74

15   mmol) was added dropwise. The mixture was stirred at 25 °C for 18 hours. The reaction mixture was poured into water and this mixture was extracted with EtOAc. The organic layer was washed with brine, dried (MgSO$_4$), filtered, and concentrated to afford 4 g of yellow oily residue. The

20   oily residue was separated by HPLC on silica gel with a mixture of hexanes and acetone (8/3, v/v) to yield 7-(2-methoxyethyl)caprolactam.

Mass spectral analysis for $C_9H_{17}N_1O_2$: $M^+H = 172$.

25

^{1}H NMR (D$_2$O): δ 3.38-3.50 (m, 3H), 3.20 (s, 3H), 2.42-2.52 (m, 1H), 2.10-2.20 (m, 1H), 1.18-1.82 (m, 8H).

Example 241 D)   To a magnetically stirred slurry of

30   Me$_3$O$^+$BF$_4^-$ in methylene chloride under nitrogen atmosphere was added the 7-(2-methoxylethyl)caprolactam product of Example 241 C. This mixture was stirred at room temperature for 3 days. The solvent was concentrated and ice-cold ammonia-saturated methanol was added and stirred

35   for 12 hours. The reaction was concentrated and the residue was dissolved in water. The pH of this aqueous solution was adjusted to pH 3 and the 2-imino, 7-

methoxyethylhexamethyleneimine product was purified on C-18
reversed phase HPLC.

Mass spectral analysis for $C_9H_{18}N_2O_1$: $M^+H = 171$.

^1H NMR (D_2O): δ 1.30- 1.82 (m, 8H), 2.35 - 2.67 (m, 2H),
3.18 (s, 3H), 3.42 (t, 3H), 3.52 (m, 1H).

Example 241 E) The 2-imino, 7-
methoxyethylhexamethyleneimine product of Example 241 D
(1.8 g, 6.6 mmol) was dissolved in acetic acid (80 mL).
Hydrobromic acid (48%, 8.9 M, 7 mL) was added and the
reaction mixture was refluxed for 12 hours under an N_2
atmosphere. After removal of all solvent under reduced
pressure, the residue was dissolved in water and purified
by C-18 reversed phase HPLC to provide 1.0 g (70% yield) of
2-imino, 7-bromoethylhexamethyleneimine.

Mass spectral analysis for $C_8H_{15}Br_1N_2$: $M^+H = 219$.

^1H NMR ($CDCl_3$): 3.68-3.75 (m, 1H), 3.36-3.56 (m, 2H),
2.60-2.65 (m, 2H), 2.42- 2.35 (m 8H).

Example 241) The product of Example 241 E (200 mg, 0.60
mmol) and N-aminomorpholine (300 mg, 3 mmol) were
dissolved in 1 ml of N,N-dimethylformamide (DMF) and
incubated at 25 °C for 7 days. The solvent was removed
by rotary evaporation under reduced pressure. The
residue was dissolved in 1 ml of water and the pH was
adjusted to pH 3.0. The solution was purified by C-18
reverse phase chromatography to give the title product
(40 mg).

Mass spectral analysis for $C_{12}H_{24}N_4O_1$: $M^+H = 241$.

^1H NMR (D_2O): δ 3.70-3.76 (t, 4H), 3.55-3.66 (m, 1H),
3.10-3.20 (t, 2H), 3.-2-3.08 (m, 4H), 2.40-2.65 (m, 2H),
1.30-1.90 (m, 8H).

Example 242

5   N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]pyridin-2-
methanamine, tris(trifluoroacetate) salt
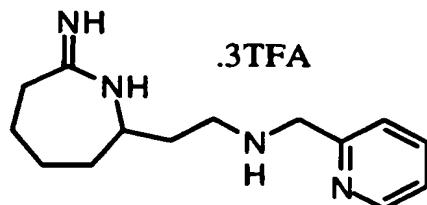
10   The product of Example 235 E (383 mg; 1 mmol) was reacted
with 2-pyridinealdehyde in 10 mL DMF (containing 0.1 mL
AcOH) in the presence of NaCNBH$_3$ for 16 hours at room
temperature. The DMF was evaporated in vacuo and the
residue was purified on preparative HPLC using AcN/H$_2$O
15   gradient (0-30% AcN in 30 minutes) affording 170 mg (55%
yield) of the title product as an oil.

Mass spectral analysis for C$_{15}$H$_{22}$N$_4$: M$^+$H = 247.

20

Example 243

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl] pyridin-3-
methanamine, tris(trifluoroacetate) salt
25
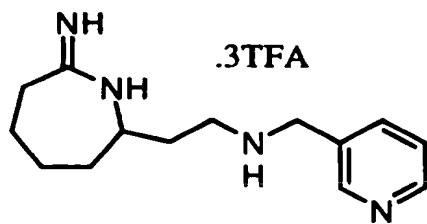
A sample of 3-pyridinealdehyde (107 mg; 1 mmol) was
reacted with the product of Example 235 E as described in
30   Example 242 to afford 175 mg (30% yield) of the title
product as an oil.

Mass spectral analysis for $C_{15}H_{22}N_4$: M^+H = 247.

Example 244

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl] pyridin-4-
methanamine, tris(trifluoroacetate) salt
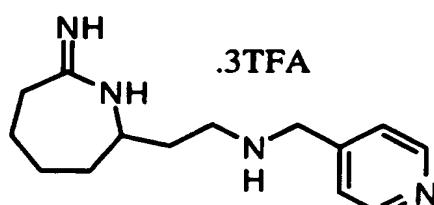
A sample of 4-pyridinealdehyde (107 mg; 1 mmol) was
reacted with the product of Example 235 E by the method
of Example 242 to afford 210 mg (36% yield) of the title
product as an oil.

Mass spectral analysis for $C_{15}H_{22}N_4$: M^+H = 247.

Example 245

1-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1H-
imidazole, bis(trifluoroacetate) salt
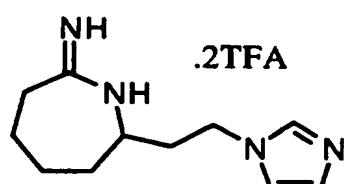
The product of Example 241 E (240 mg, 0.72 mmol) and
imidazole (700 mg, 10.2 mmol) were dissolved in 0.5 ml
of N,N-dimethylformamide (DMF) and incubated at 50 °C for
1 day. The solvent was removed by rotary evaporation
under reduced pressure. The residue was dissolved in 1

ml of water and the pH was adjusted to pH 3.0. The solution was purified by C-18 reverse phase chromatography to give the title product (200 mg).

5   Mass spectral analysis for $C_{11}H_{18}N_4$: $M^+H = 207$.

^1H NMR (D_2O): δ 8.62 (s, 1H), 7.60 (s, 1H), 7.55 (s, 1H), 4.20-4.25 (t,1H), 3.20-3.40 (m, 2H), 2.40-2.65 (m,2H), 1.30-2.20 (m, 8H).

10

Example 246

1-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1H-1,2,4-
15   triazole, bis(trifluoroacetate) salt

The product of Example 241 E and 1,2,4-triazole were
20   reacted by the method of Example 245 to provide 65 mg of the title product.

Mass spectral analysis for $C_{10}H_{17}N_5$: $M^+H = 208$.

25   ^1H NMR (D_2O): δ 9.02 (s, 1H), 8.30 (s, 1H), 4.25-4.40(t,2H0, 3.90-3.94 (t, 1H), 3.40-3.60 (m, 2H), 1.10-2.60 (m, 8H).

30   Example 247

4-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-4H-1,2,4-
triazole, bis(trifluoroacetate) salt
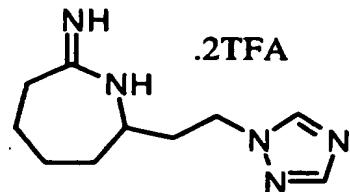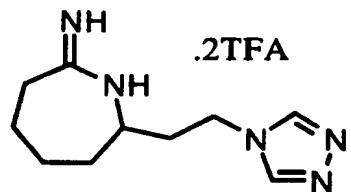
The product of Example 241 E and 1,2,4-triazole were
reacted by the method of Example 245 to provide 32 mg of
the title product.

Mass spectral analysis for $C_{10}H_{17}N_5$: $M^+H = 208$

^1H NMR (D_2O): δ 9.02 (s, 2H), 4.20-4.26 (t, 2H), 3.50-
3.62 (m, 2H), 3.00-3.05 (m, 1H), 1.20- 2.60 (m, 8H)

Example 248

1-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1H-
tetrazole, trifluoroacetate salt
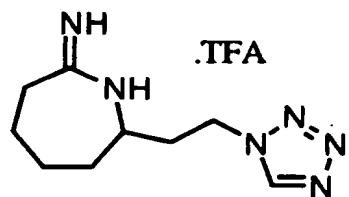
The product of Example 241 E and 1H-tetrazole were
reacted by the method of Example 245 to provide 50 mg of
the title product.

Mass spectral analysis for $C_9H_{16}N_6$: $M^+H = 209$.

^1H NMR (D$_2$O): δ 8.60 (s, 1H), 4.72-4.80 (m, 3H), 3.40-
3.47 (m, 2H), 1.20-2.60 (m, 8H).

Example 249

methyl 1-[2-(hexahydro-7-imino-1H-azepin-2-
yl)ethyl]pyrrolidine-2-carboxylate,
bis(trifluoroacetate) salt
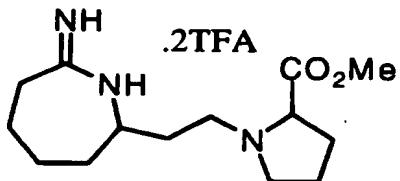
The product of Example 241 E and L-proline methyl ester
hydrochloride were reacted by the method of Example 245
to provide 30 mg of the title product.

Mass spectral analysis for $C_{14}H_{25}N_3O_2$: $M^+H = 268$.

^1H NMR (D_2O): δ 4.22-4.32 (t, 1H), 3.70 (s, 3H), 3.50-
3.60 (m, 2H), 2.96-3.05 (m, 2H), 2.40-2.62(m, 2H), 1.15-
2.05 (m, 12H).

Example 250

4-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]morpholine,
bis(trifluoroacetate) salt
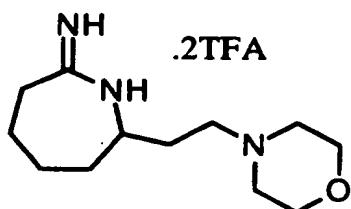
The product of Example 241 E and morpholine were reacted
by the method of Example 245 to provide 12 mg of the
title product.

Mass spectral analysis for $C_{12}H_{23}N_3O_1$: $M^+H = 226$.

^{1}H NMR (D$_2$O): δ 3.95-4.02 (m, 2H), 3.52-3.72 (m, 3H), 3.35-3.45 (m, 2H), 3.00-3.19 (4H), 2.40-2.65(m, 2H), 1.30-2.05 (m, 8H).

Example 251

1-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]piperazine, bis(trifluoroacetate) salt
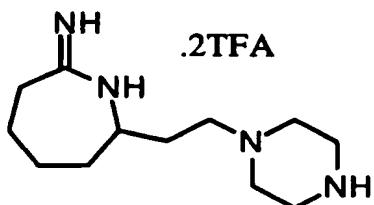
The product of Example 241 E and piperazine were reacted by the method of Example 245 to provide 370 mg of the title product.

Mass spectral analysis for C$_{12}$H$_{24}$N$_4$: M$^+$H = 225.

^{1}H NMR (D$_2$O): δ 3.55-3.65 (m, 1H), 3.45-3.54 (m, 8H), 3.22-3.30 (t, 2H), 2.40-2.65(m, 2H), 1.30-2.10 (m, 8H).

Example 252

1-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-4-methylpiperazine, tris(trifluoroacetate) salt
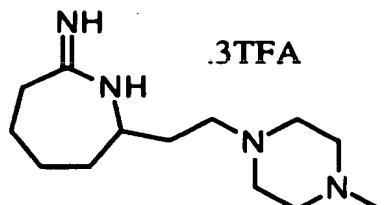
The product of Example 241 E and 1-methylpiperazine were
reacted by the method of Example 245 to provide 60 mg of
the title product.

5   Mass spectral analysis for $C_{13}H_{26}N_4$: $M^+H = 239$.

Example 253

10   hexahydro-7-(2-nitro-1-phenyl)-2H-azepin-2-imine,
trifluoroacetate salt
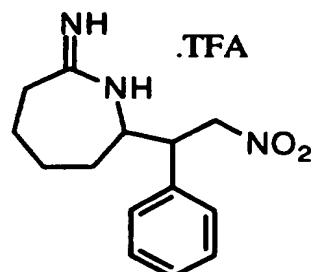
15   Example 253 A)   A sample of 2-nitrostyrene (2 g; 13.4
mmol) in 5 mL AcN was cooled to -10 °C and 1-
morpholinocyclohexene was added to the solution under N_2.
The temperature was raised to 25 °C over a 1 hour period
and the solvent was then removed in vacuo. The residue
20   was dissolved in 15 mL MeOH and 5 mL of 1N HCl were added
to the solution and it was refluxed gently for 15
minutes. The product precipitated, filtered and dried,
yielding 1.6 g (54% yield) of 2-(2-Nitro-1-
phenylethyl)cyclohexanone as a white solid.

25
Mass spectral analysis for $C_{14}H_{17}N_1O_3$: $M^+H = 248$ and M^+Li
= 254.

Example 253 B)   The 2-(2-Nitro-1-
30   phenylethyl)cyclohexanone product of Example 253 A (2.47
g; 10 mmol) underwent a Beckmann Rearrangement when
allowed to react with H_2N-OSO_3H (1.24 g; 11 mmol) in 20

mL formic acid. Purification yielded 2.1 g (80% yield)
7-[(2-Nitro-1-phenyl)ethyl]caprolactam as a white solid.

Mass spectral analysis for $C_{14}H_{18}N_2O_3$: M^+H = 263.

Example 253) The 7-[(2-Nitro-1-phenyl)ethyl]caprolactam
product of Example 253 B was converted to the amidine via
the method of Example 228 C to afford 0.85 g (78% yield)
of the title compound as a white solid.

Mass spectral analysis for $C_{14}H_{19}N_3O_2$: M^+H = 262.

^1H NMR (D_2O): δ 7.40-7.20 (m,5H); 5.00-4.70 (m,2H); 3.95-
3.85 (m,1H); 2.80-2.45 (m,2H); 1.85-1.05 (m,6H).

                              Example 254

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)-2-
phenylethyl]guanidine, bis(trifluoroacetate) salt
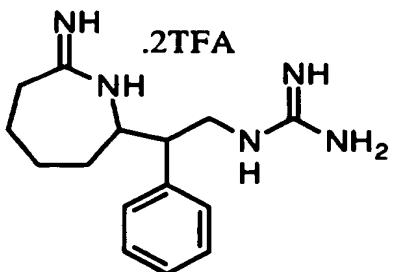
The product of Example 205 (459 mg; 1 mmol) was reacted
with formamidine sulfonic acid (124 mg; 1 mmol) in 15 mL
MeOH in the presence of N,N-diisopropylethylamine (DIPEA)
(0.38 mL, 2 mmol) for 18 hours. The MeOH solvent was
evaporated and the residue purified on preparative HPLC
using AcN/H_2O gradient (0-30% AcN in 30 minutes),
affording 380 mg (75% yield) of the title product as a
white solid.

Mass spectral analysis for $C_{15}H_{23}N_5$: M^+H = 274.

Example 255

5   hexahydro-N-(hexahydro-1H-azepin-2-ylidene)-7-imino-β-
phenyl-1H-azepine-2-ethanamine, bis(trifluoroacetate)
salt

10
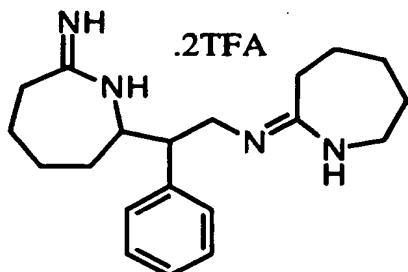
The product of Example 205 was allowed to react with 1-
aza-2-methoxy-1-cycloheptene by the method of Example 236
to afford 320 mg (58% yield) of the title product as a
white solid material.

15

Mass spectral analysis for $C_{20}H_{30}N_4$: $M^+H = 327$.

^{1}H NMR (D_2O): 7.40-7.10 (m,5H); 3.95-3.85 (t,J=7Hz,1H);
3.60-3.35 (m,2H); 3.20-3.00 (m,3H); 2.80-2.60 (m,1H);
20   2.55-2.40 (m,1H); 2.35-2.10 (m,2H); 1.85-1.00 (m,12H).

Example 256

25   hexahydro-7-(2-nitro-1-phenylpropyl)-2H-azepin-2-imine,
trifluoroacetate salt
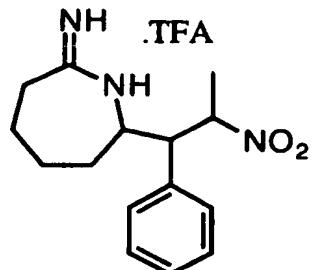
A sample of 2-methyl-2-nitrostyrene was reacted with 1-morpholinocyclohexene by the method of Example 253 A and the resulting intermediate was converted by the
5 subsequent procedures of Example 253 to 600 mg (68% yield) of the title product as a white solid.

Mass spectral analysis for $C_{15}H_{21}N_3O_2$: $M^+H = 276$.

10 ^{1}H NMR (D_2O): δ 7.40-7.05 (m,5H); 4.22-4.10, 4.00-3.90, 3.80-3.70, 3.50-3.30 (m,2H); 2.80-2.45 (m,2H); 1.90-1.10 (m,9H).

15   Example 257

hexahydro-7-imino-α-methyl-β-phenyl-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt

20
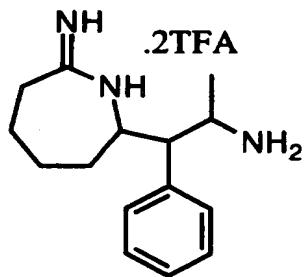
Isomer-1

The product of Example 256 (600 mg; 2.2 mmol) was reduced via catalytic hydrogenation in 25 mL EtOH. The crude
25 product was purified as described in Example 205 to afford two diastereomers. The first eluting peak #1 afforded 135 mg (31% yield) of the title Isomer-1 as a white solid.

30 Mass spectral analysis for $C_{15}H_{23}N_3$: $M^+H = 246$.

¹H NMR (D₂O): δ 7.40-7.17 (m,5H); 4.10-4.00 (m,1H); 3.85-3.70 (m,1H); 3.07-2.96 (m,1H); 2.80-2.65 (m,1H); 2.50-2.35 (m,1H); 1.90-1.70 (m,3H); 1.60-1.00 (m,6H).

5

Example 258

hexahydro-7-imino-α-methyl-β-phenyl-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt

10
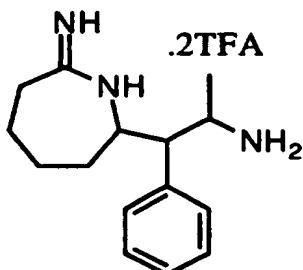
Isomer-2

The product of Example 256 (600 mg; 2.2 mmol) was reduced
15   via catalytic hydrogenation in 25 mL EtOH. The crude
product was purified as described in Example 257 to
afford two diastereomers. The second eluting peak #2
afforded 120 mg (22% yield) of the title Isomer-2 as a
white solid.
20
Mass spectral analysis for C₁₅H₂₃N₃: M⁺H = 246.

¹H NMR (D₂O): δ 7.40-7.15 (m,5H); 4.10-4.00 (m,1H); 3.85-3.70 (m,1H); 3.30-3.20 (m,1H); 2.85-2.70 (m,1H); 2.60-
25   2.45 (m,1H); 1.90-1.55 (m,2H); 1.50-1.30 (m,3H); 1.30-1.05 (m,4H).

Example 259

30
hexahydro-7-imino-α-methyl-β-cyclohexyl-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt
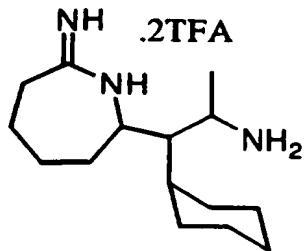
The product of Example 253 (240 mg; 0.88 mmol) was
hydrogenated in 20 mL EtOH (5% HCl) for two days in the
presence of 300 mg PtO_2. Work up and purification
afforded 110 mg (53% yield) of the title product as a
white solid.

Mass spectral analysis for $C_{14}H_{27}N_3$: $M^+H = 238$.

Example 260

7-[1-(1,3-benzodioxol-5-yl)-2-nitropropyl]hexahydro-2H-
azepin-2-imine, trifluoroacetate salt
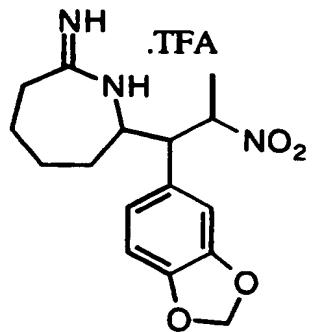
A sample of 3,4-dioxomethylene-1-nitrostyrene (3.86 g; 20
mmol) was reacted with 1-morpholino-1-cyclohexene in 25
mL AcN by the method of Example 253 A and the resulting
intermediate was converted by the subsequent procedures
of Example 253 to 1.25 g (74% yield) of the title product
as a white solid.

Mass spectral analysis for $C_{15}H_{19}N_3O_4$: $M^+H = 306$.

^{1}H NMR (D$_2$O): 6.80-6.65 (m,3H); 5.85 (s,2H);4.95-4.70 (m,2H); 3.90-3.80 (m,1H); 3.70-3.60 (m,1H); 2.70-2.45 (m,2H); 1.80-1.10 (m,6H).

Example 261

β-(1,3-benzodioxol-5-yl)hexahydro-7-imino-α-methyl-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt
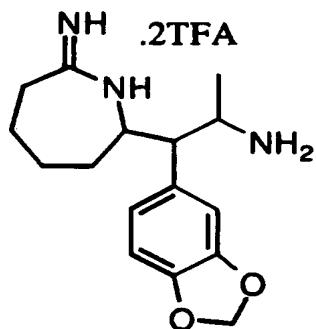
The product of Example 260 (600 mg; 1.43 mmol) was reduced and purified as described in Example 205. Purification of the crude product afforded 420 mg (58% yield) of the title material as a white solid.

Mass spectral analysis for C$_{15}$H$_{21}$N$_3$O$_2$: M$^+$H = 276.

^{1}H NMR (D$_2$O): δ 6.85-6.70 (m,3H); 5.90 (s,2H); 3.82-3.70 (m,1H); 3.42-3.30 (m,1H); 3.20-3.00 (m,2H); 2.80-2.40 (m,2H); 1.85-1.05 (m,6H).

Example 262

hexahydro-7-[2-nitro-1-(2-thienyl)ethyl]-2H-azepine, trifluoroacetate salt

NH
‖
  NH
      .TFA

      NO₂

   S
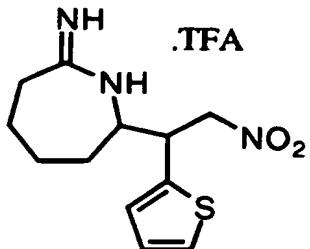
A sample of 2-(2-nitrovinyl)thiophene (3.1 g; 20 mmol)
was reacted with 1-morpholino-1-cyclohexene in 20 mL AcN
5   by the method of Example 253 A and the resulting
intermediate was converted by the subsequent procedures
of Example 253 to 1.1 g (47% yield) of the title product
as a white solid.

10   Mass spectral analysis for $C_{12}H_{17}N_3O_2S$: $M^+H = 268$.

^1H NMR (CDCl$_3$): δ 10.00 (br,1H); 9.85 (br,1H); 8.45
(br,1H); 7.35-6.95 (m,3H); 5.20-5.00 (m,1H); 4.90-4.75
(m,1H); 4.30-4.10 (m,1H); 3.70-3.50 (m,1H); 2.70-2.50
15   (m,1H); 2.40-2.25 (m,1H); 2.10-1.90 (m,2H); 1.85-1.25
(m,4H)

Example 263

20

hexahydro-7-imino-β-(2-thienyl)-1H-azepine-2-ethanamine,
bis(trifluoroacetate) salt

NH
‖
  NH
      .2TFA

      NH₂

   S

25
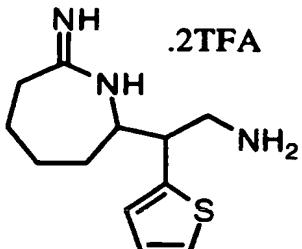
The product of Example 262 (600 mg; 1.57 mmol) was
reduced and purified as described in Example 205 to

afford 390 mg (73% yield) of the title product as a white solid.

Mass spectral analysis for $C_{12}H_{19}N_3S$: $M^+H = 238$.

^1H NMR (D_2O): δ 7.45-7.32 (m,1H); 7.10-7.05 (m,1H); 7.05-6.95 (m,1H); 3.95-3.40 (m,4H); 2.70-2.20 (m,2H); 2.00-1.20 m,6H).

Example 264

hexahydro-7-imino-β-(3-thienyl)-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt
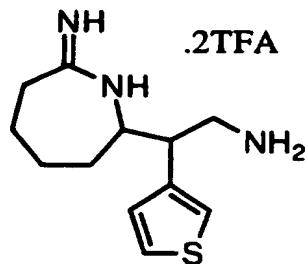
A sample of 3-(2-nitrovinyl)thiophene (3.1 g; 20 mmol) was reacted with 1-morpholino-1-cyclohexene in 10 mL AcN by the method of Example 253 A and the resulting intermediate was converted by the subsequent procedures of Example 253 and Examples 205 to afford 380 mg (78% yield) of the title product as a white solid.

Mass spectral analysis for $C_{12}H_{19}N_3S$: $M^+H = 238$.

^1H NMR (D_2O): 7.50-7.40 (m,1H); 7.40-7.30 (m,1H); 7.05-7.00 (m,1H); 3.90-3.75 (m,1H); 3.60-3.50 (m,3H); 2.75-2.40 (m,2H); 1.8501.60 (m,2H); 1.60-1.30 (m,3H); 1.30-1.05 (m,1H).

Example 265

hexahydro-7-imino-β-(2-furanyl)-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt

5
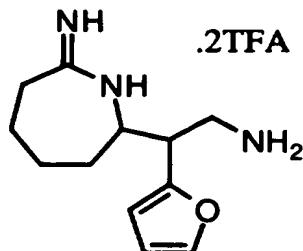
2-(2-nitrovinyl)furan (1.39 g; 10 mmol) was reacted with 1-morpholino-1-cyclohexene in 25 mL AcN by the method of

10 Example 253 A and the resulting intermediate was converted by the subsequent procedures of Example 253 and Examples 205 to 140 mg (48% yield) of the title product as a white solid.

15 Mass spectral analysis for $C_{12}H_{19}N_3O_1$: $M^+H = 222$.

^{1}H NMR (D$_2$O): δ 7.42 (s,1H);6.45-6.30 (m,2H); 3.90-3.80 (m,1H); 3.40-3.22 (m,3H); 2.70-2.40 (m,2H); 1.90-1.70 (m,2H); 1.60-1.10 (m,4H).

20

Example 266

hexahydro-N-(hexahydro-1H-azepin-2-ylidene)-7-imino-β-

25 (2-thienyl)-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt
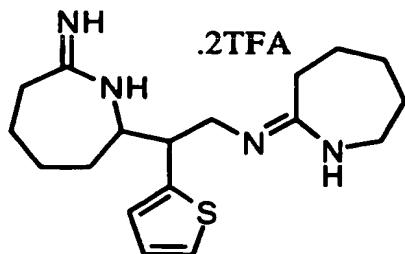
The product of Example 263 (23 mg; 0.5 mmol) was reacted with 1-aza-2-methoxy-1-cycloheptene (127 mg; 0.5 mmol) and the product was isolated as described in Example 236 to afford 225 mg (80% yield) of the title product as a

5   white solid.

Mass spectral analysis for $C_{18}H_{28}N_4S$: $M^+H = 333$.

^1H NMR (D_2O): 7.35-7.25 (m,1H); 7.00-6.90 (m,2H); 4.25-
10   3.75 (m,2H); 3.60-3.40 (m,1H); 3.35-3.15 (m,2H); 2.80-
2.60 (m,1H); 2.60-2.05 (m,4H); 1.90-1.10 (m,12H).

Example 267

15

hexahydro-7-imino-N-(2-pyrrolidinylidene)-β-(2-thienyl)-
1H-azepine-2-ethanamine, bis(trifluoroacetate) salt

20
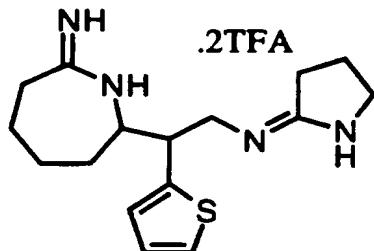
The product of Example 263 (100 mg; 0.21 mmol) was reacted with 2-methoxy-pyrrolidine (99 mg; 1 mmol) as described in Example 236 to afford 80 mg (71% yield) of the title product as a white solid.

25

Mass spectral analysis for $C_{16}H_{24}N_4S$: $M^+H = 305$.

Example 268

30

hexahydro-7-[1-(1H-indol-3-yl)-2-nitroethyl]-2H-azepin-
2-imine, trifluoroacetate salt
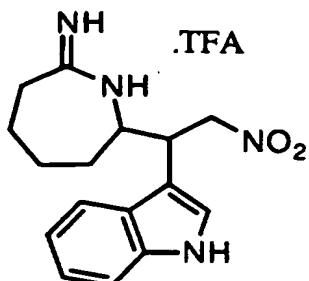
3-(2-nitrovinyl)indole (500 mg; 2.6 mmol) was reacted
with 1-morpholino-1-cyclohexene (0.5 g; 3 mmol) in 5 mL
5   AcN by the method of Example 253 A and the resulting
intermediate was converted by the subsequent procedures
of Example 253 to afford 255 mg (65% yield) of the title
product as a light yellow solid.

10   Mass spectral analysis for $C_{16}H_{20}N_4O_2$: M+H = 301.

^{1}H NMR (D$_2$O): δ 7.60 (d,J=8Hz,1H); 7.40 (d,J=8Hz,1H);
7.22 (s,1H); 7.18-7.00 (m,2H); 5.00-4.80 (m,2H); 4.08-
3.90 (m,2H); 2.70-2.40 (m,2H); 1.80-1.15 (m,6H).
15

Example 269

hexahydro-7-imino-β-(1H-indol-3-yl)-1H-azepine-2-
20   ethanamine, bis(trifluoroacetate) salt
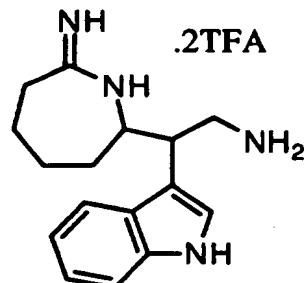
A sample of Example 268 (255 mg; 0.62 mmol) was reduced
25   and purified as described in Example 205. Purification
afforded 120 mg (52% yield) of the title product as a
white solid.

Mass spectral analysis for $C_{16}H_{22}N_4$: M+H = 271.

^{1}H NMR (D$_2$O): δ 7.60 (d,J=8Hz,1H); 7.45 (d,J=8Hz,1H);
7.33 (s,1H); 7.22-7.00 (m,2H); 4.10-3.95 (m,1H); 3.60-
3.30 (m,2H); 3.20-3.00 (m,1H); 2.80-2.35 (m,2H); 2.00-
1.00 (m,6H).

Example 270

hexahydro-7-[(2-nitrophenyl)methyl]-2H-azepin-2-imine,
monohydrochloride
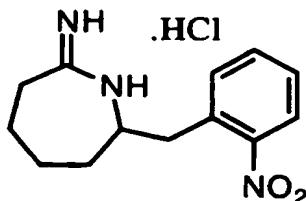
Example 270 A)   Commercially available (Shanghai
Institute of Organic Chemistry) 7-(2-nitrobenzyl)
caprolactam (0.50 g, 2.01 mmol) was dissolved in CH$_2$Cl$_2$
(25 mL, 0.1 M solution) and treated with triethyloxonium
tetrafluoroborate (0.57 g, 3.02 mmol) by the method of
Example 3 to give 0.68 g of the crude ethyl iminoether
product.
Example 270)   The product of Example 270 A was dissolved
in methanol (25 mL, 0.1 M solution) and treated with
ammonium chloride (0.20 g, 3.73 mmol) by the method of
Example 4 to give 0.36 g title material.

Elemental analysis: $C_{13}H_{17}N_3O_2$. 1.05 HCl . 0.50 H$_2$O (MW =
294.59).

	C	H	N	Cl
Calculated:	53.00	6.52	14.26	12.64
Found:	53.22	6.45	13.94	12.61

Example 271

2-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]benzenamine,
dihydrochloride

5
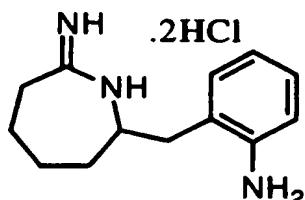
The product of Example 270 (0.150 g, 0.59 mmol) was
dissolved in ethanol and treated with 5 % Palladium on
10   Carbon under 5 psi of Hydrogen to give the title product
(141 mg, 0.46 mmol).

Elemental analysis: $C_{13}H_{19}N_3$. 2.00 HCl . 1.00 H_2O (MW =
308.25).

	C	H	N	Cl
Calculated:	50.65	7.52	13.63	23.00
Found:	50.99	7.47	13.44	22.90

15

Example 272

2-[(hexahydro-7-imino-1H-azepin-2-
20   yl)methyl]cyclohexanamine, dihydrochloride
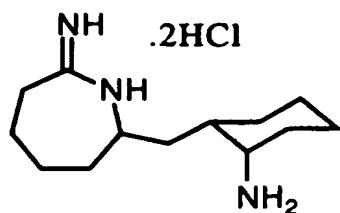
The product of Example 270 (0.262 g, 0.9 mmol) was
25   dissolved in ethanol, treated with 5 % Rhodium on Carbon
under 60 psi of Hydrogen and warmed to 60°C to give the
title product (66 mg, 0.22 mmol).

Elemental·analysis: $C_{13}H_{25}N_3$. 2.00 HCl . 1.00 H_2O (MW = 308.25).

	C	H	N	Cl
Calculated:	46.28	8.64	12.12	24.16
Found:	46.25	8.24	12.30	24.25

5   Example 273

hexahydro-7-[(4-nitrophenyl)methyl]-2H-azepin-2-imine, monohydrochloride

10
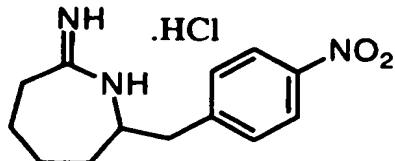
Example 273 A) Commercially available (Shanghai Institute of Organic Chemistry) 7-(p nitrobenzyl)caprolactam (1.1 g, 4.6 mmol) dissolved in 50
15   mL of CH_2Cl_2 was treated with $Me_3O^+BF_4^-$ (0.7 g, 4.6 mmol) by the method of Example 3 to give 850 mg of its imino ether.
Example 273) The imino ether product of Example 273 A (0.83 g, 3.2 mmol) in 50 mL of MeOH was reacted with
20   NH_4Cl (0.15 g, 2.9 mmol) by the method of Example 4 to give 0.77 g (87%) of the title material.
HRMS (EI) calcd for $C_{13}H_{17}N_3O_2$ m/e 247.132, found m/e 247.132

25   Elemental analysis: $C_{13}H_{17}N_3O_2$. 1.2 HCl . 0.9 H_2O (MW = 307.26).

	C	H	N	Cl
Calculated:	50.82	6.56	13.68	13.85
Found:	50.54	6.33	13.85	14.14

Example 274

4-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]benzenamine,
dihydrochloride
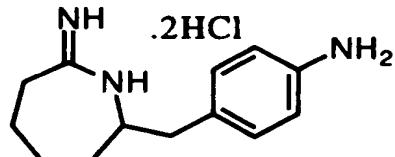
5

The product from Example 273 (0.55 g, 1.8 mmol) in 30 mL
of EtOH was reduced with 5% Palladium on carbon under 5
psi of hydrogen. Solvent removal in vacuo followed by
10 lyophilization in water gave 0.46 g (97%) of the title
material.
HRMS (EI) calcd for $C_{13}H_{19}N_3$ m/e 217.158, found m/e 217.158

Elemental analysis: $C_{13}H_{19}N_3$. 1.1 HCl . 0.4 H_2O (MW =
15 266.45).

	C	H	N	Cl
Calculated:	58.60	7.93	15.77	15.30
Found:	58.46	7.54	15.72	15.17

Example 275

hexahydro-7-[[4-(trifluoromethyl)phenyl]methyl]-2H-
20 azepin-2-imine, monohydrochloride
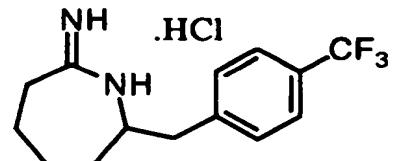
Example 275 A) Commercially available (Shanghai institute
25 of Organic Chemistry) 7-(p
trifluoromethylbenzyl)caprolactam (0.9 g, 3.4 mmol)
dissolved in 50 mL of CH_2Cl_2 was treated with $Me_3O^+BF_4^-$
(0.5 g, 3.4 mmol) by the method of Example 3 to give 835
mg of its imino ether.

Example 275) The imino ether product of Example 275 A (0.78 g, 2.7 mmol) in 50 mL of MeOH was reacted with NH_4Cl (0.13 g, 2.5 mmol) by the method of Example 4 to give 0.45 g (56%) of the title material.

5 HRMS (EI) calcd for $C_{14}H_{17}N_2F_3$ m/e 270.139, found m/e 270.137

Elemental analysis: $C_{14}H_{17}N_2F_3$. 1.0 HCl . 0.75 H_2O (MW = 320.27).

	C	H	N	Cl
Calculated:	52.50	6.14	8.75	11.56
Found:	52.31	6.18	8.71	11.36

10

Example 276

7-[(4-fluorophenyl)methyl]hexahydro-2H-azepin-2-imine,
15 monohydrochloride
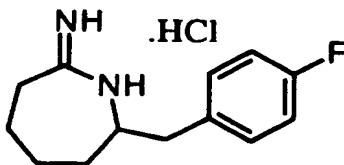
Example 276 A)   Commercially available (Shanghai
20 institute of Organic Chemistry) 7-(p-fluorobenzyl)
caprolactam (1.3 g, 6.0 mmol) dissolved in 50 mL of
CH_2Cl_2 was treated with $Me_3O^+BF_4^-$ (1.2 g, 7.8 mmol) by
the method of Example 3 to give 1.3 g of its imino ether.
Example 276)   The imino ether product of Example 276 A
25 (1.2 g, 5.1 mmol) in 25 mL of MeOH was reacted with NH_4Cl
(0.26 g, 4.9 mmol) by the method of Example 4 to give 1.1
g of the title material.

Elemental analysis: $C_{13}H_{17}N_2F$. 1.0 HCl . 0.75 H_2O (MW =
30 270.26).

	C	H	N	Cl
Calculated:	57.77	7.27	10.37	13.12

Found: 57.80   7.39   10.34   13.43

Example 277

5   hexahydro-7-[[3-(trifluoromethyl)phenyl]methyl]-2H-
azepin-2-imine, monohydrochloride
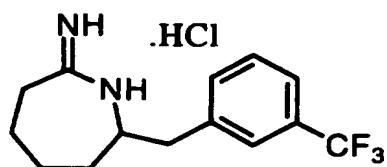
10   Example 277A)   Commercially available 7-(3-
trifluoromethylphenylmethyl) caprolactam (Shanghai Institute
of Organic Chemistry, 1.12 g, 3.5 mmol) was treated with
trimethyloxonium tetrafluoroborate (1.11 g, 5.3 mmol) in
CH_2Cl_2 (10 mL) by the method of Example 3, to yield its
15   iminoether derivative (1.23 g) as a thick oil.
Example 277)   A solution of the imino ether product of
Example 277A (1.20 g, 3.5 mmol) in MeOH (12 mL) was reacted
with ammonium chloride (0.17 g, 3.1 mmol) by the method of
Example 5. The residue after removal of solvent was
20   subjected to lyophilization in water to generate the title
material (1.27 g).

Elemental analysis: $C_{14}H_{17}N_2F_3 \cdot$ 1 HCl $\cdot$ 0.55 H_2O (MW=316.36)

	C	H	N	Cl
Calculated:	53.10	6.08	8.85	11.20
Found:	53.18	6.00	8.46	11.33

Example 278

30

7-[(2,4-difluorophenyl)methyl]hexahydro-2H-azepin-2-
imine, monohydrochloride
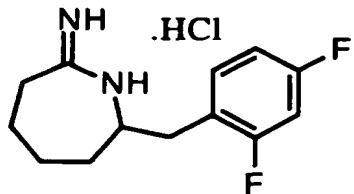
Example 278 A)   7-(2'-4'-difluorobenzyl)caprolactam
(Shanghai Institute of Organic Chemistry, 1.24 g, 5.2
mmol) was dissolved in CH_2Cl_2 (25 mL) under an argon
atmosphere. To this was added trimethyloxonium
tetrafluoroborate ($Me_3O^+BF_4^-$) and the reaction was
carried out by the method of Example 3. The residue was
purified by flash column chromatography (80%
hexane/acetone) to generate 950 mg (72%) of clean imino
ether.

Example 278 B)   The imino ether product of Example 278 A
(910 mg, 3.6 mmol) and NH_4Cl in MeOH (10 mL) were reacted
by the method of Example 5. After removing all solvent
in vacuo, the residue was dissolved in H_2O (40 mL) and
washed once with EtOAc (20 mL). The aqueous layer was
then lyophilized twicw from water to give the title
compound.

Elemental analysis: $C_{13}H_{16}N_2F_2$. 1 HCl . 0.5 H_2O (MW =
283.75).

	C	H	N
Calculated:	55.03	6.39	9.87
Found:	55.08	6.57	9.66

Example 279

7-[(2,6-dichlorophenyl)methyl]hexahydro-2H-azepin-2-
imine, monohydrochloride
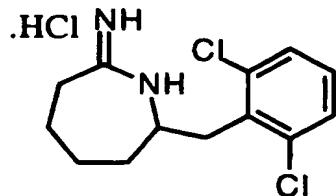
Example 279 A) Commercially available (Shanghai
Institute of Organic Chemistry) 7-(2,6-dichlorobenzyl)
caprolactam (0.50 g, 1.84 mmol) was dissolved in CH2Cl2
(25 mL, 0.1 M solution) and treated with triethyloxonium
tetrafluoroborate (0.52 g, 2.76 mmol) by the method of
Example 3 to give 0.56 g of the crude ethyl iminoether
product.

Example 279 B) The ethyl iminoether product of Example
279 A was dissolved in methanol (25 mL, 0.1 M solution)
and treated with ammonium chloride (0.150 g, 2.79 mmol)
by the method of Example 4 to give 0.58 g of the title
material.

Elemental analysis: C13H16N2Cl2 . 0.9 HCl . 0.75 H2O (MW =
317.52).

	C	H	N	Cl
Calculated:	49.18	5.84	8.82	32.38
Found:	49.47	5.64	8.57	32.32

Example 280

hexahydro-7-[3-(2-thienyl)-2-propenyl]-2H-azepin-2-
imine, monohydrochloride
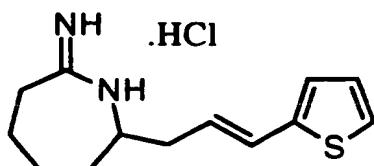
Example 280 A) Palladium acetate (0.063 g, 0.28 mmol)
and tri-o-tolylphosphine (0.170 g, 0.56 mmol) were
combined in a 250 mL round bottom flask under nitrogen.

To this was added triethylamine (1.62 g, 16 mmol) and 2-
bromothiophene (2.55 g, 15.6 mmol). After this mixture
was stirred for 5 min., the Isomer B title product of
Example 18 (7-allylcaprolactam, 2.17 g, 14.2 mmol) was
5   added along with 5 mL of Acetonitrile. The reaction
mixture was refluxed for 2 h. before 10 mL of
acetonitrile was added and the mixture was refluxed
overnight. The cooled mixture was partition between 75
mL of saturated NaHCO₃ and 100 mL of EtOAc and then
10 chromatographed to produce 1.7 g (67 mmol) of product.
Example 280 B) The product of Example 280 A (1.0 g, 4.26
mmol) was dissolved in 50 mL of CH2Cl2 and treated with
trimethyloxonium tetrafluoroborate (0.82 g, 5.5 mmol) by
the method of Example 3. This produced 1.11 g of the
15 methyl imino ether.
Example 280) The methyl imino ether product of Example
280 B (0.88 g, 3.53 mmol) was treated with ammonium
chloride (0.17 g, 3.18 mmol) and methanol (50 mL, 0.05 M
solution) by the method of Example 4 to produce 0.68 g
20 (71%) of title product.

Elemental analysis: C₁₃H₁₈N₂S . 1.1 HCl . 0.4 H₂O . 0.3
NH₄Cl (MW = 297.72).

	C	H	N	Cl
Calculated:	52.45	7.14	10.82	16.67
Found:	52.21	7.02	11.10	16.40

25

Example 281

methyl α-[[(3,4-dihydro-2H-pyrrol-5-
yl)amino]methyl]hexahydro-7-imino-1H-azepine-2-acetate,
30 bis(trifluoroacetate) salt

NH .2TFA

NH HN N

CO₂Me
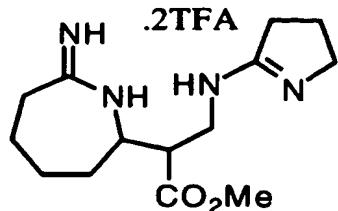
Example 281 A)   Methyl, 2-iodo-3-nitropropionate
(prepared as in Org. Synth. VI, 799 (1988)) is allowed to
5   react with the morpholine enamine of cyclohexanone to
afford after mild hydrolysis, 2-[1-methoxycarbonyl-2-
nitroethyl]cyclohexanone.
Example 281 B)   The 2-[1-methoxycarbonyl-2-
nitroethyl]cyclohexanone product of Example 281 A is
10   converted via a Beckmann Rearrangement to a substituted
caprolactam. Isolation and purification affords the 7-
[1-methoxycarbonyl-2-nitroethyl]caprolactam.
Example 281 C)   The 7-[1-methoxycarbonyl-2-
nitroethyl]caprolactam product of Example 281 B is
15   converted to the corresponding amidine via the method of
Example 228c to afford 7-[1-methoxycarbonyl-2-
nitroethyl]homoiminopiperidine.
Example 281 D)   The 7-[1-methoxycarbonyl-2-
nitroethyl]homoiminopiperidine product of Example 281 C
20   is reduced via catalytic hydrogenation as in the method
of Example 205 to afford 7-[1-methoxycarbonyl-2-
aminoethyl]homoiminopiperidine.
Example 281)   The 7-[1-methoxycarbonyl-2-
aminoethyl]homoiminopiperidine product of Example 281 D
25   is allowed to react with 2-methoxypyrroline by the method
of example 236 to afford the title product.

Example 282

30

4,5-dihydro-5-[(hexahydro-7-imino-1H-azepin-2-
yl)methyl]isoxazole-3-carboxylic acid, monohydrochloride
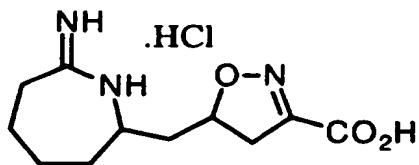
A solution of 0.2 g (0.00048 mol) of the product of
Example 283 in 18.5 mL of water, 25 mL of acetone and 7.5

5   mL of conc. HCl was heated at reflux for 44 hours. After
all solvent was removed in vacuo, the residue was
dissolved in water and lyophilized to afford the title
product as a yellow foam.

10   ^{1}H NMR(D_2O): δ 1.25-2.0 (m, 8H), 2.4-2.7 (m, 2H), 2.85
(m, 1H), 3.3 (m, 1H), 3.7 (m, 1H), 4.9 (m, 1H).

Mass spectral analysis for $C_{11}H_{17}N_3O_3$: $M^+H = 240$.

15

Example 283

ethyl 4,5-dihydro-5-[(hexahydro-7-imino-1H-azepin-2-
yl)methyl]isoxazole-3-carboxylate, trifluoroacetate salt

20
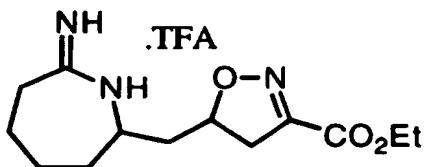
Example 283 A) The Isomer B title product of Example 18
(7-allyl caprolactam, 7 g, 0.046 mol) was reacted with

25   13.9 g (0.092 mol) of ethyl chlorooximidoacetate in 700
mL of toluene. This mixture was stirred at reflux for 18
hours. The reaction mixture was allowed to cool and then
concentrated to afford 13 g of a brown oil.
Chromatography (silica gel, EtOAc) afforded 10.5 g of 7-

30   [[4,5-dihydro-3-(ethoxycarbonyl)isoxazol-5-yl]methyl]
hexahydro-1H-azepin-2-one as an off-white solid.

Mass spectral analysis for $C_{13}H_{20}N_2O_4$: $M^+H = 269$

Example 283) To a magnetically stirred slurry of 1.16 g
(0.0078 mol) of $Me_3O^+BF_4^-$ and 20 mL of CH_2Cl_2 under
5   nitrogen (N_2) was added 2 g (0.0075mol) of the 7-[[4,5-
dihydro-3-(ethoxycarbonyl)isoxazol-5-yl]methyl]
hexahydro-1H-azepin-2-one product of Example 283 A. This
mixture was stirred at room temperature for 18 hours
before it was diluted with 30 mL of EtOAc and partitioned
10   between the organic layer and 40 mL of saturated $NaHCO_3$.
The organic phase was separated, dried ($MgSO_4$), filtered,
and concentrated under reduced pressure to provide 1.6 g
of the iminoether as a yellow oil. The iminoether (1.6
g, 0.0057 mol) and 0.3 g (0.0057 mol) of ammonium
15   chloride (NH_4Cl) were refluxed in 25 mL of methanol
(MeOH) under a nitrogen atmosphere for 22 hours. After
cooling the reaction to room temperature, it was filtered
and partitioned between 25 mL of water and 7 mL of EtOAc.
The aqueous phase was washed with a 15 mL portion of
20   EtOAc before lyophilization to provide 1.3 g of a dark
foam. Chromatographic purification of this material on a
preparatory C-18 column eluting with acetonitrile/water
afforded after lyophilization, 1.1 g of the title
compound as a dark oil.
25
Mass spectral analysis for $C_{13}H_{21}N_3O3$: $M^+H = 268$.

Further chromatographic separations (C-18,
acetonitrile/water) were successful in separating two
30   diastereomers.

(slow eluting diastereomer)

^{1}H NMR(D_2O): δ 1.15 (t, 3H), 1.25-2.0 (m, 8H), 2.4-2.7
35   (m, 2H), 2.85 (m, 1H), 3.3 (m, 1H), 3.7 (m, 1H), 4.2 (q,
2H), 4.9 (m, 1H).

(fast eluting diastereomer)

^{1}H NMR(D_2O): δ 1.15 (t, 3H), 1.25-2.0 (m, 8H), 2.4-2.7 (m, 2H), 2.85 (m, 1H), 3.3 (m, 1H), 3.7 (m, 1H), 4.2 (q, 2H), 4.95 (m, 1H).

Example 284

4,5-dihydro-5-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]isoxazole-3-carboxamide, trifluoroacetate salt
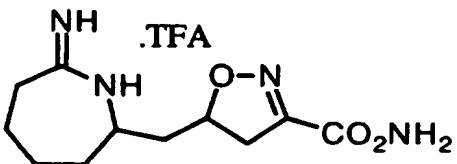
A solution of 0.1 g (0.00024 mol) of the product of Example 283 in 10 mL of methanol (saturated with anhydrous ammonia) was capped and heated at 60 °C for 18 hours. After all solvent was removed in vacuo, the residue was dissolved in water and lyophilized to afford the title product as a yellow foam.

^{1}H NMR(D_2O): δ 1.25-2.0 (m, 8H), 2.4-2.7 (m, 2H), 2.85 (m, 1H), 3.3 (m, 1H), 3.7 (m, 1H), 4.9 (m, 1H).

Mass spectral analysis for $C_{11}H_{18}N_4O_1$: M^+H = 239.

Example 285

3-amino-5-[(hexahydro-7-imino-1H-azepine-2-yl)methyl]-tetrahydrofuran-2-one, bis(trifluoroacetate) salt
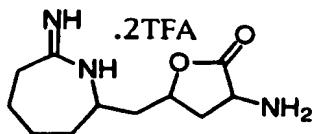
To a solution of 0.1 g (0.00024 mol) of the product of
Example 283 (prior to diastereomer separation) in 10 mL
of methanol was added 0.02 g palladium/carbon (10%).
5   This mixture was pressurized under 50 psi H_2 and stirred
for 3 days at 25 °C. Filtration and concentrated gave a
colorless oil. Chromatography (C-18, acetonitrile/water)
afforded 30 mg of the title compound as a white solid.

10   ^{1}H NMR (D_2O): δ 1.2-2.1(m, 9H), 2.45 (m, 1H), 2.6 (m,
1H), 32.8 (m, 1H), 3.75 (m, 2H), 4.4 (m, 1H).

Mass spectral analysis for $C_{11}H_{19}N_3O_2$: M^+H = 226.

15

Example 286

7-[2-(2,2-dimethyldioxolan-4-yl)ethyl]hexahydro-2H-
azepin-2-imine, monohydrochloride

20
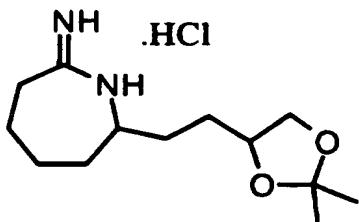
Example 286 A) Sodium hydride, 60% in mineral oil (8,3
g, 200 mmol) was washed with 2 portions of hexane and
25   then dried under an N_2 flow. This material was suspended
in DMF and ethyl 2-cyclohexanonecarboxylate (34.1 g, 200
mmol) was added slowly under N_2 with cooling with a 25 °C
water bath. After complete addition, the mixture was
stirred at 25 °C for ~1 hour and 4-bromo-1-butene (35.1
30   g, 260 mmol) and tetrabutylamonium iodide (2.0 g) were
added. The stirring mixture was heated to 50 °C for 18
hours (overnight). The reaction was then cooled to room
temperature. The entire mixture was poured into water,
neutralized with dilute HCl, and extracted with two

portions of 1:1 ether-hexane The combined organics were
then washed with two portions of water and saturated
brine, dried over MgSO4, filtered and stripped giving
41.8 g of an impure mixture of products. Purification of
5   the product by chromatography (silica gel, : 5 % methyl
t-butyl ether / 90 % hexane) gave 28.4 g of 2-(1-
butenyl)-2-carboethoxycyclohexanone.
Example 286 B)   The product of Example 286 A (11.2 g, 50
mmol), lithium chloride (10.6 g, 250 mmol), water (0.99
10   g, 55 mmol), and DMSO (250 mL) were combined under N2 and
refluxed for 2 hours. The reaction was then cooled to 25
°C. The reaction mixture was poured into water and
extracted with two portions of 1:1 ether - hexane. The
organic phases were combined and washed with two portions
15   water followed by saturated brine and then dried over
MgSO4. After filtering and stripping, the product was
purified by fractional distillation at 1.5 mm Hg. (The
product boils at 65 to 70 °C at 1 to 2 mm Hg.), giving
5.5 g of 2-(1-butenyl) cyclohexanone.
20   Example 286 C)   The 2-(1-butenyl)cyclohexanone product of
Example 286 B (7.70 g, 51 mmol) was converted to its oxime
by the method of Example 1 using 5.3 g (76 mmol) of
hydroxylamine hydrochloride and 7.0 g (85 mmol) of NaOAc in
a mixture of 70 mL of ethanol and 70 mL of water. The
25   procedure produced 8.48 g of the 2-(1-butenyl)cyclohexanone,
oxime as a white solid.
Example 286 D)   The product of Example 286 C (4.2 g, 25
mmol) was converted to the title compound mixture of two
regioisomers by the method of Example 18 using 4.6 g (26
30   mmol) of benzene sulfonylchloride. The crude product
mixture was triturated with Et2O to give 1.8 g of 7-(1-
butenyl)-hexahydro-1H-azepin-2-one (Isomer A). The filtrate
was concentrated to provide a mixture of isomers but
predominately Isomer A. This mixture is separated into its
35   Isomer-A and Isomer-B (3-(1-butenyl)-hexahydro-1H-azepin-2-
one) components by chromatography.
Example 286 E)   The Isomer-A title product of Example 286 D
(15.2 g, 91 mmol) was reacted with di-t-butyl dicarbonate

(25.8 g, 118 mmol) and DMAP (1.55 g, 12.6 mmol) in 350 mL
THF to give 20.9 g (86%) of the the N-BOC derivative by the
method of Example 285.

Example 286 F) The product from Example 286 E (3.46 g, 13
5 mmol) was dissolved in a 1:1 mixture of acetone and water
and treated with osmium tetraoxide (3.0 mL, 2.5 equivalent
%) and 4-methylmorpholine oxide (3.1 g, 26.4 mmol) by the
method of Example 212 A. The combined organic extracts were
then dried (Na2SO4), stripped and purified by column
10 chromatography on silica gel to yield (2.98 g, 76%) of (3,4-
dihydroxybutyl)-hexahydro-1H-azepin-2-one.

Example 286 G) The product from Example 286 F (2.18 g) was
treated with 2 mL trifluoroacetic acid in 20 mL CH2Cl2 for
30 min., and stripped *in vacuo*. Then, 25 mL toluene was
15 added along with 12 mL 2,2-dimethoxypropane and 100 mg p-
toluenesulfonic acid and brought to reflux for 4 hours. The
mixture was cooled and partitioned between ether and dilute
aqueous sodium bicarbonate. The organic layer was the
washed with brine, dried (sodium sulfate), stripped and
20 purified by column chromatography on silica gel to yield
(0.98 g) of (3,4-dihydroxyacetonylbutyl)-hexahydro-1H-
azepin-2-one.

Example 286 H) The product from Example 286 G (0.44 g,
1.3 mmol) was reacted with trimethyloxonium
25 tetrafluoroborate (0.27 g, 1.8 mmol) by the method of
Example 3 to yield 0.46 g (100%) of its methyl imino
ether derivative.

Example 286) The product of Example 286 H (0.31 g, 0.87
mmol) in 3 mL of MeOH was reacted with ammonium chloride (43
30 mg, 0.8 mmol) by the method of Example 5 to yield 0.38 g of
hexahydro-7-(1,2-acetonylbutyl)-1H-azepin-2-imine,
monohydrochloride.

^{1}H NMR (CD3OD): 4.2-4.0 (m, 2H), 3.65 (m, 1H), 3.55 (t,
35 1H) 2.85 - 2.55 (m, 2H), 2.1 - 1.5 (m, 10H), 1.4 -1.3 (d,
6H)

Example 287

hexahydro-7-[2-(4-pyridinyl)ethyl]-2H-azepin-2-imine,
monohydrochloride

5
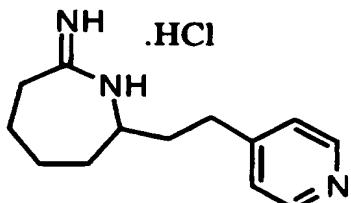
The title compound was prepared from 4-vinylpyridine and
cyclohexanone by the methods described in Example 290.

10

Mass spectral analysis for $C_{13}H_{19}N_3$: M^+H = 218.

^1H NMR (D_2O): δ 8.52 (d, J = 7 Hz, 2H); 7.80 (d, J = 7
Hz, 2H); 3.60 - 3.45 (m, 1H); 3.00 - 2.80 (m, 2H); 2.68 -
15   2.38 (m, 2H); 2.00 - 1.63 (m, 5H); 1.60 - 1.20 (m, 3H).

Example 288

20   4-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]pyridinium-
1-oxide, bis(trifluoroacetate) salt
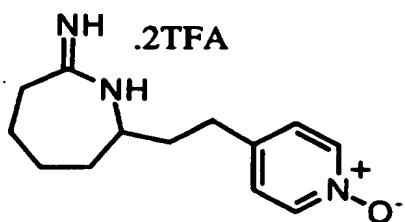
25   To the product of Example 287 (500 mg, 1.7 mmol)
dissolved in a pH 5 phosphate buffer (50 mL) and ethanol
(50 mL) was added oxone (2.1 g, 3.5 mmol). The reaction
contents were stirred for 3 days and lyophilized. The
residue was purified by C-18 reverse phase chromatography
30   eluting with a CH_3CN/H_2O (0.05% TFA) gradient to give the
title material as a white solid (350 mg, 60% yield).

Mass spectral analysis for $C_{13}H_{19}N_3O$: $M^+H = 234$.

^1H NMR (D_2O): δ 8.20 (d, J = 7Hz, 2H); 7.45 (d, J = 7Hz,
2H); 3.50 - 3.40 (m, 1H); 2.80 - 2.60 (m, 2H); 2.60 -
2.35 (m, 2H); 2.00 - 1.60 (m, 5H); 1.60 - 1.20 (m, 3H).

Example 289

4-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1-
methylpyridinium chloride, monohydrochloride salt
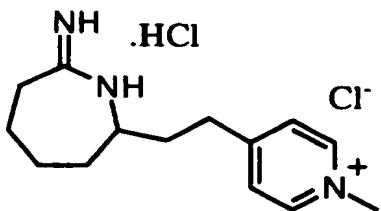
Hexahydro-7-[2-(4-pyridyl) ethyl]-1H-azepin-2-one was
prepared as described in Example 290 by the condensation
of 4-vinylpyridine with cyclohexanone. The title
material was prepared from this hexahydro-7-[2-(4-
pyridyl) ethyl]-1H-azepin-2-one as described in Example
291.

Mass spectral analysis for $C_{14}H_{22}N_3$: $M^+H = 232$.

^1H NMR (D_2O): δ 8.48 (d, J = 7 Hz, 2H); 7.75 (d, J = 7
Hz, 2H); 4.20 (s, 3H); 3.60 - 3.40 (m, 1H); 3.00 - 2.80
(m, 2H); 2.65 - 2.40 (m, 2H); 2.00 - 1.65 (m, 5H); 1.60 -
1.20 (m, 3H).

Example 290

hexahydro-7-[2-(2-pyridinyl)ethyl]-2H-azepin-2-imine,
monohydrochloride
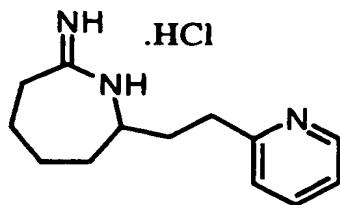
Example 290 A)   A sample of 1-Pyrrolidino-1-cyclohexene
(7.1 mL, 44 mmol) and 2-vinylpyridine (4.3 mL, 40 mmol)
were refluxed overnight in diglyme (100 mL). Water was
then added and the mixture was stirred an additional 2
hours before extracting it with Et$_2$O. The ether layer
was dried over MgSO$_4$ and concentrated in vacuo leaving an
oil. The residue oil was distilled on a kugelrohr
apparatus at 60-80 °C (0.1 mm) to give 2-(2-pyridyl)
ethyl-2-cyclohexanone as a yellow oil (6.5 g).
Example 290 B)   The 2-(2-Pyridyl) ethyl-2-cyclohexanone
product of Example 290 A (6.6 g, 32 mmol) in formic acid
(99%, 200 mL) was added dropwise to hydroxylamine-O-
sulfonic acid (2.0 g, 36 mmol) in formic acid (200 mL).
The exothermic reaction was stirred overnight and
concentrated in vacuo. The residue was partitioned
between CH$_2$Cl$_2$ and water. The aqueous layer was
neutralized to pH 5.5 with 50% NaOH and extracted with
CH$_2$Cl$_2$ which was dried over MgSO$_4$ and concentrated in
vacuo leaving an oil (3.5 g) which solidified. The solid
was recrystallized from EtOAc to give hexahydro-7-[2-(2-
pyridyl) ethyl]-1H-azepin-2-one as a light amber solid
(1.6 g). The filtrate contained a mixture of hexahydro-
7-[2-(2-piperidyl) ethyl]-1H-azepin-2-one and hexahydro-
3-[2-(2-pyridyl)ethyl]-1H-azepin-2-one. The isomers were
separated by chromatography on silica gel eluting with
60% acetone/hexanes. The first component to elute was
hexahydro-3-[2-(2-pyridyl) ethyl]-1H-azepin-2-one and the
second to elute was hexahydro-7-[2-(2-pyridyl) ethyl]-1H-
azepin-2-one.

Example 290) To the hexahydro-7-[2-(2-pyridyl) ethyl]-1H-azepin-2-one product component of Example 290 A (684 mg, 3 mmol) in CH_3CN (20 mL) was added dropwise

phosphorous oxychloride (0.6 mL, 6 mmol). The contents
5   were stirred overnight and then concentrated in vacuo. The residue was taken up in methanol (10 mL) and anhydrous ammonia was bubbled into the solution. The reaction was stoppered and stirred overnight. The reaction mixture was concentrated in vacuo and the
10   residue dissolved in 1N HCl and lyophilized. The lyophilized material was purified by C18 reverse phase chromatography eluting with a CH_3CN/H_2O (0.05% TFA)

gradient to give a solid. This solid was dissolved in 1N HCl and lyophilized to provide the title material as a
15   white solid (220 mg).

Mass spectral analysis for $C_{13}H_{19}N_3$: $M^+H = 218$.

^1H NMR (D_2O): δ 8.50 (d, J = 7 Hz, 1H); 8.40 (t, J = 7
20   Hz, 1H); 7.85 - 7.75 (m, 2H); 3.60 - 3.50 (m, 1H); 3.10 - 3.00 (m, 2H); 2.70 - 2.40 (m, 2H); 2.10 - 1.70 (m, 5H); 1.60 - 1.25 (m, 3H).

25   Example 291

2-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1-methylpyridinium chloride, bis(trifluoroacetate) salt
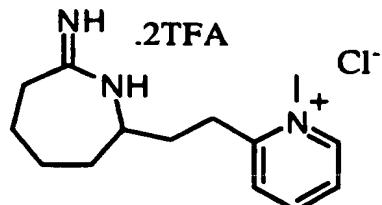
30

The Hexahydro-7-[2-(2-piperidyl) ethyl]-1H-azepin-2-one product component of Example 290 A (1.7 g, 8 mmol) was converted to the amidine via the method of Example 228c

to afford a white solid. The solid was dissolved in 1N HCl and lyophilized to afford the title material as a white solid (1.1 g, 45% yield).

5   Mass spectral analysis for $C_{14}H_{22}N_3$: $M^+H = 232$.

^1H NMR (D_2O): δ 8.60 (d, J = 7 Hz, 1H); 8.32 (t, J = 7 Hz, 1H); 7.82 (d, J = 7 Hz, 1H); 7.77 (t, J = 7 Hz, 1H); 4.20 (s, 3H); 3.75 - 3.60 (m, 1H); 3.20 - 3.00 (m, 2H); 10 2.75 - 2.40 (m, 2H); 2.15 - 1.95 (m, 2H); 1.95 - 1.75 (m, 3H); 1.70 - 1.30 (m, 3H).

Example 292

15

hexahydro-7-[2-(1-methylpiperidin-2-yl)ethyl]-2H-azepin-2-imine, dihydrochloride

20
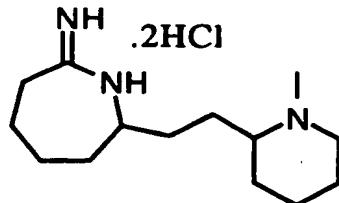
The product of Example 291 (300 mg, 1 mmol), platinum oxide (200 mg), H_2O (5 mL) and HOAc (30 mL) were shaken on a Parr hydrogenator at 55 psi of hydrogen overnight. Filtration and concentration in vacuo gave a colorless 25 oil (490 mg). The oil was purified by C-18 reverse phase chromatography eluting with a CH_3CN/H_2O (0.05% TFA) gradient to give a white solid. The solid was dissolved in 1N HCl and lyophilized to afford the title material as a white solid (285 mg, 92% yield).

30

Mass spectral analysis for $C_{14}H_{27}N_3$: $M^+H = 238$.

^{1}H NMR (D$_2$O): δ 3.55 − 3.40 (m, 1H); 3.40 − 3.25 (m, 1H); 3.15 − 2.80 (m, 2H); 2.70 (s, 3H); 2.65 − 2.35 (m, 2H); 2.00 − 1.20 (m, 16H).

5

Example 293

hexahydro-7-[2-(2-piperidinyl)ethyl]-2H-azepin-2-imine, dihydrochloride

10
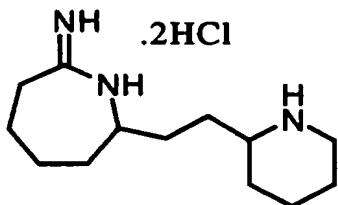
The product of Example 290 (138 mg, 0.5 mmol), platinum oxide (100 mg), conc HCl (0.5 mL) and ethanol (30 mL)
15 were shaken on a Parr hydrogenator at 55 psi of hydrogen overnight. Filtration and concentration in vacuo gave a colorless oil. The oil was purified by C-18 reverse phase chromatography eluting with a CH$_3$CN/H$_2$O (0.05% TFA) gradient to give a white solid. The solid was dissolved
20 in 1N HCl and lyophilized to afford the title product as a colorless foam (81 mg, 55% yield).

Mass spectral analysis for C$_{13}$H$_{25}$N$_3$: M$^+$H = 224.

25 ^{1}H NMR (D$_2$O): δ 3.60 − 3.40 (m, 1H); 3.35 − 3.20 (m, 1H); 3.05 − 2.92 (m, 1H); 2.90 − 2.75 (m, 1H); 2.70 − 2.50 (m, 1H); 2.50 − 2.40 (m, 1H); 2.00 − 1.00 (m, 16H).

30 ## Example 294

hexahydro-7-[2-(4-piperidinyl)ethyl]-2H-azepin-2-imine, dihydrochloride
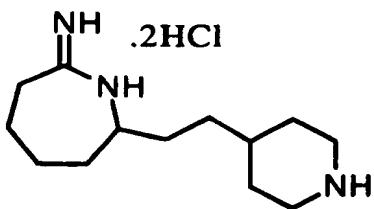
The title material was prepared by the method of Example 293 from the product of Example 287.

Mass spectral analysis for $C_{13}H_{25}N_3$: $M^+H = 224\cdot$

^{1}H NMR (D_2O): δ 3.45 - 3.35 (m, 1H); 3.30 - 3.15 (m, 2H); 2.85 - 2.70 (m, 2H); 2.60 - 2.30 (m, 2H); 1.90 - 1.10 (m, 15H).

Example 295

hexahydro-7-[2-(4-piperidinyl)ethyl]-2H-azepin-2-imine, dihydrochloride
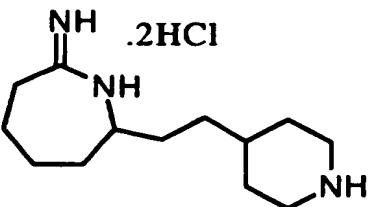
The title material was prepared by the procedure of Example 292 from the product of Example 289.

Mass spectral analysis for $C_{14}H_{27}N_3$: $M^+H = 238$.

^{1}H NMR (D_2O): δ 3.50 - 3.25 (m, 3H); 2.90 - 2.70 (m, 2H); 2.67 (s, 3H); 2.65 - 2.32 (m, 2H); 1.90 - 1.60 (m, 5H); 1.60 - 1.10 (m, 10H).

Example 296

hexahydro-7-[2-[1-(methylsulfonyl)piperidin-2-yl]ethyl]-
2H-azepin-2-imine, trifluoroacetate salt
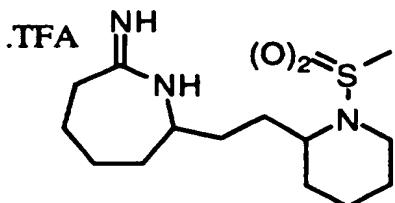
Example 296 A) A sample of the Hexahydro-7-[2-(2-
pyridyl) ethyl]-1H-azepin-2-one product of Example 290b
(2.4 g, 11 mmol), platinum oxide (500 mg) and glacial
acetic acid (30 mL) were shaken on a Parr hydrogenator at
55 psi of hydrogen overnight. The contents were filtered
and the filtrate was concentrated in vacuo. The residue
was dissolved in water and adjusted to pH 9 with 2.5N
NaOH. The aqueous solution was extracted with CH_2Cl_2 and
the organic layer was dried over $MgSO_4$ and concentrated
in vacuo leaving hexahydro-7-[2-(2-piperidyl)ethyl]-1H-
azepin-2-one as a white solid (2.3 g).
Example 296 B) To the hexahydro-7-[2-(2-piperidyl)
ethyl]-1H-azepin-2-one product of Example 296 A (2.3 g,
10 mmol) in anhydrous pyridine (8 mL) and CH_2Cl_2 (4 mL)
was added dropwise methanesulfonyl chloride (0.74 mL) in
CH_2Cl_2 (2 mL). The contents were stirred overnight,
concentrated in vacuo and partitioned between CH_2Cl_2 and
water. The CH_2Cl_2 layer was dried over $MgSO_4$ and
concentrated in vacuo leaving an oil. The oil was
purified by C18 reverse phase chromatography eluting with
a CH_3CN/H_2O (0.05% TFA) gradient to give hexahydro-7-[2-
(2-methylsulfonylpiperidyl)ethyl]-1H-azepin-2-one (1.5
g).
Example 296) The title product was prepared from the
hexahydro-7-[2-(2-methylsulfonylpiperidyl)ethyl]-1H-
azepin-2-one product of Example 296 B by the method
described in Example 291.

Mass spectral analysis for $C_{14}H_{27}N_3O_2S$: $M^+H = 302$.

^1H NMR (D_2O): δ 3.85 - 3.70 (m, 1H); 3.60 - 3.40 (m, 2H);
3.05 - 2.90 (m, 1H); 2.95 (s, 3H); 2.70 - 2.35 (m, 2H);
1.90 - 1.20 (m 16H).

Example 297

3-(hexahydro-7-imino-1H-azepin-2-yl)-1-(4-morpholinyl)propan-1-one, trifluoroacetate salt
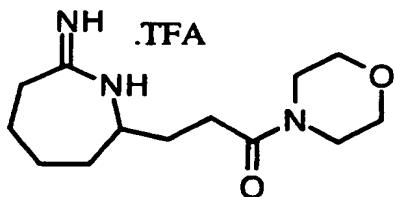
Example 297 A) A sample of Cyclohexanone-2-propionic
acid was coupled with morpholine in the presence of TBTU
(6.4 g; 20 mmol) and 3.5 mL (20 mmol) DIPEA in 25 mL DMF
for 2 hours. The DMF was removed in vacuo and the
product (4.4 g; 18.4 mmol) was isolated on preparative
HPLC using AcN/H_2O gradient (10-50% AcN in 30 minutes).

Example 297 B) The product of Example 297 A was
converted to its lactam by the method of Example 253b to
afford 1.3 g (28% yield) of the lactam as a white solid.

Example 297) This lactam product of Example 297 B was
converted by the method of Example 228c to 810 mg (62%
yield) of the title amidine product as a solid.

Mass spectral analysis for $C_{13}H_{23}N_3O_2$: $M^+H = 254$.

Example 298

6-(phenylmethyl)piperidin-2-imine, monohydrochloride

$$\text{NH} \quad .\text{HCl}$$
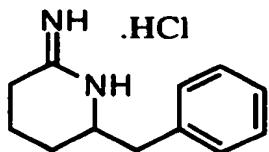
Example 298 A)   A sample of 2-benzylpyridine (Aldrich,
2.5 g, 0.015 mole), sodium amide (780 mg, 0.02 mole) and
5   N, N-dimethylaniline (25 mL) were refluxed overnight.
The contents were allowed to cool and were partitioned
between ether and water. The ether layer was dried
(MgSO4) and concentrated in vacuo leaving an oil. The
oil was purified by chromatography. The purified
10   material was dissolved in 1N HCl, lyophilized, and
triturated with EtOAc to give 2-amino-6-benzylpyridine as
a white solid.
Example 298)   A sample of the 2-amino-6-benzylpyridine
product of Example 298 A was reduced in acetic acid under
15   hydrogen atmosphere utilizing 5% Rh/C catalyst to afford
2-imino-6-benzylpiperidine as an oil. The oil was
purified by C-18 reverse phase chromatography to give a
white solid. The solid was dissolved in 1 N HCl,
lyophilized, and recrystallized from EtOH/EtOAc to give
20   the title product as a white solid.

Mass spectral analysis for $C_{12}H_{16}N_2$: $M^+H = 189$.

^{1}H NMR (CDCl3): δ 9.85 (s, 1H); 8.95 (s, 1H); 8.62 (s,
25   1H); 7.40 - 7.10 (m, 5H); 3.80 - 3.60 (m, 1H); 3.20 -
3.00 (m, 1H); 2.90 - 2.70 (m, 2H); 2.65 - 2.45 (m, 1H);
2.42 - 2.25 (m, 2H); 1.92 (m, 2H); 1.75 (m, 1H); 1.50 -
1.35 (m, 1H).

30

Example 299

6-(cyclohexylmethyl)piperidin-2-imine, monohydrochloride
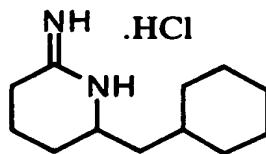
The 2-amino-6-benzylpyridine product of Example 298 A was
reduced in acetic acid under hydrogen atmosphere

5   utilizing platinum oxide catalyst to afford 2-imino-6-
cyclohexylmethylpiperidine as an oil. The oil was
dissolved in 1 N HCl and lyophilized to give a white
solid. The solid was recrystallized from EtOAc to give
the title product as white crystals.

10
Mass spectral analysis for $C_{12}H_{22}N_2$: $M^+H = 195$.

^{1}H NMR (CDCl$_3$): δ 9.60 (s, 1H); 8.90 (s, 1H); 8.70 (s,
1H); 3.60 - 3.40 (m, 1H); 2.90 - 2.70 (m, 1H); 2.70 -

15   2.50 (m, 1H); 2.10 - 1.80 (m, 2H); 1.80 - 1.00 (m, 13H);
1.00 - 0.80 (m, 2H).

Example 300

20

trans-N-[3-(5-imino-3-methylpyrrolidin-2-
yl)ethyl]phenylmethylamine, dihydrochloride
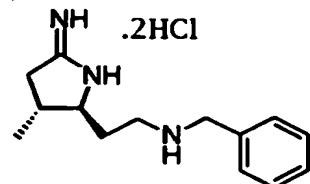
25

Example 300 A)   *cis* and *trans*-5-[(1,3-dioxolan-2-yl)methyl]-
4-(methyl)pyrrolidin-2-one was prepared in the manner
described (R. Ohrlein, W. Schwab, R. Ehrler, V. Jager,
Synthesis 1986, 535-538) starting with 1,1-dimethoxy-3-

30   nitropropane and methyl crotonate.
Example 300 B)   To a stirring solution of the product of
Example 300A (1.0 g, 5.3 mmol) in 40 mL CHCl$_3$ was added

20 mL H$_2$O and 10 mL TFA. After stirring for 2 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc. The organic layer was washed with a minimum of saturated NaHCO$_3$, dried over

5   MgSO$_4$, filtered, and concentrated under reduced pressure to recover 0.75 g of crude aldehyde.

Example 300 C and D) To a sirring solution of product of Example 300 B (0.75 g, 5.3 mmol) and benzylamine (0.62 g, 5.8 mmol), in 20 mL MeOH was added NaBH$_3$CN (0.17 g, 2.7

10   mmol). The reaction was maintained at pH 4 by the addition of HOAc. After stirring for three days, the reaction mixture was concentrated under vacuum. To the residue was added 1 N HCl and EtOAc. After separating the layers, the aqueous phase was neutralized with NaHCO$_3$

15   and extracted with EtOAc. After concentrating the organic phase, the residue was treated with 1 N HCl and lyophilized. The resulting solid was purified by reverse phase column chromatography on a C-18 column. The cis (300 C) and trans (300 D) lactams were separated.

20   Example 300 E) The product of Example 300 D (0.28 g, 1.2 mmol) was treated with trimethyloxonium tetrafluoroborate (0.21 g, 1.4 mmol) in CH$_2$Cl$_2$ (DCM, 10 mL) by the method of Example 3, to yield 0.19 g.

Example 300) A solution of the product of Example 300 E

25   (0.19 g, 0.78 mmol) in MeOH (10 mL) was reacted with ammonium chloride (0.05 g, 0.93 mmol) by the method of Example 5 followed by chromatography on reverse phase HPLC to generate the title material 300 (0.10 g).

30   Elemental analysis: C$_{14}$H$_{21}$N$_3$ · 1.86 HCl 1 H$_2$O (MW=317.17)

	C	H	N	Cl
Calculated:	53.02	7.90	13.25	20.79
Found:	52.67	7.87	12.90	20.44

Example 301

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-4,5-
dihydro-1H-imidazol-2-amine, bis(trifluoroacetate) salt
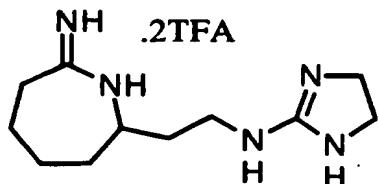
N-Boc-2-methylthio-2-imidazoline (0.46 g; 2 mmol) was
combined with the 7-(2-aminoethyl)homoiminopiperidine
product of Example 235 E (0.383 g; 1 mmol) in 20 mL MeOH
and the mixture was stirred for 24 hours at room
temperature. The solvent was removed in vacuo and the
residue was redissolved in 20 mL CH_2Cl_2/TFA (1:1). After
30 minutes of stirring, the solvents were evaporated in
vacuo and the title compound was isolated on preparative
HPLC to afford 320 mg (71% yield) of the title product as
a white solid.

Mass spectral analysis for $C_{11}H_{21}N_5$: M^+H = 224.

^1H NMR (D_2O): δ 3.58 (m, 5H); 3.16 (m, 2H); 2.72-2.40 (m,
2H); 1.90-1.20 (m, 8H)

Example 302

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1,4,5,6-
tetrahydropyrimidin-2-amine, bis(trifluoroacetate) salt
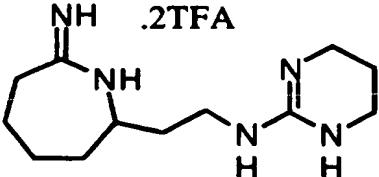
N-Boc-(3,4,5,6-tetrahydro)-2-methylthio-2-pyrimidine
(0.46 g; 2 mmol) was reacted with the 7-(2-
aminoethyl)homoiminopiperidine product of Example 235 E

(0.383 g; 1 mmol) in 20 mL MeOH by the method of Example 301 to afford 280 mg (60% yield) of the title product as a white hygroscopic solid.

5   Mass spectral analysis for $C_{12}H_{23}N_5$: M^+H = 238.

^{1}H NMR (D_2O): δ 3.56 (m, 1H); 3.18 (m, 4H); 3.06 (m, 2H); 2.68-2.38 (m, 2H); 1.96-1.20 (m, 10H).

10

Example 303

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-3,4-
dihydro-4-methyl-2H-pyrrol-5-amine,
15   bis(trifluoroacetate) salt
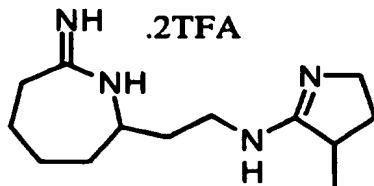
Example 303 A)   A sample of 3-Methyl-2-pyrrolidinone
20   (Aldrich, 5 g, 50 mmol) and Lawesson's Reagent (10 g, 25
mmol) were added to 120 ml of toluene and refluxed for 3
hours. After rotary evaporation, the residue was
dissolved in methylene chloride and purified by silica
gel column chromatography to afford 3-Methyl-2-
25   pyrrolidinethione as a solid.

Mass spectral analysis for $C_5H_9N_1S_1$: M^+H = 116.

Example 303 B)   The 3-Methyl-2-pyrrolidinethione product
30   of Example 303 A (1.7 g, 17 mmol) and methyl iodide (3.3
g, 20 mmol) were dissolved in acetone and stirred at 25
°C for 12 hours. After rotary evaporation, the residue
was dissolved in EtOAc and extracted with water. The
EtOAc fraction was dried over magnesium sulfate and
35   filtered. The filtrate was evaporated and the residue was

triturated with hexanes to afford 3-Methyl-2-
methylthiopyrroline as a solid.

Mass spectral analysis for $C_6H_{11}N_1S_1$: M$^+$H = 130.

Example 303) The 7-(2-aminoethyl)homoiminopiperidine
product of Example 235 E (0.6 g, 4.3 mmol) and the 3-
methyl, 2-methylthio-pyrrroline product of Example 303 B
(0.3 g, 2.2 mmol) were dissolved in acetonitrile (5 ml)
and stirred under a nitrogen atmosphere for 12 hours.
After rotary evaporation, the residue was dissolved in
water and washed with Et2O. The aqueous fraction was
lyophilized and the residue was dissolved in 0.05% TFA
and purified on C18-reversed phase HPLC.

Mass spectra analysis of $C_{13}H_{24}N_4$: M$^+$H = 237.

^{1}H NMR (D$_2$O): δ 1.10-1.20 (d, 3H), 1.30- 2.65 (m, 13H),
2.90 - 3.70 (m, 5H).

Example 304

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-3,4-
dihydro-2-methyl-2H-pyrrol-5-amine,
bis(trifluoroacetate) salt
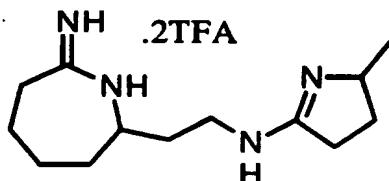
Example 304 A) A sample of 5-Methyl-2-pyrrolidinone
(Aldrich, 5 g, 50 mmol) and Lawesson's Reagent (10 g, 25
mmol) were added to 120 ml of toluene and refluxed for 3
hours. After rotary evaporation, the residue was
dissolved in methylene chloride and purified by silica

gel column chromatography to afford 5-Methyl-2-pyrrolidinethione as a solid.

Mass spectral analysis for $C_5H_9N_1S_1$: M^+H = 116.

Example 304 B)   The 5-Methyl-2-pyrrolidinethione product of Example 304 A (1.7 g, 17 mmol) and methyl iodide (3.3 g, 20 mmol) were dissolved in acetone and stirred at 25 °C for 12 hours. After rotary evaporation, the residue was dissolved in EtOAc and washed with water. The EtOAc fraction was dried over magnesium sulfate and filtered. The filtrate was evaporated and the residue was triturated with hexanes to afford 5-methyl-2-methylthiopyrroline as a solid.

Mass spectral analysis for $C_6H_{11}N_1S_1$: M^+H = 130.

Example 304)   A sample of the 7-(2-aminoethyl)homoiminopiperidine product of Example 235e (0.6 g, 4.3 mmol) and the 5-methyl, 2-methylthio-pyrrroline product of Example 304 B (0.3 g, 2.2 mmol) were dissolved in acetonitrile (5 ml) and stirred under nitrogen atmosphere for 12 hours. After rotary evaporation, the residue was dissolved in water and washed with Et$_2$O. The aqueous fraction was lyophilized and the residue was dissolved in 0.05% TFA and purified on C18-reversed phase HPLC to provide the title product.

Mass spectra analysis of $C_{13}H_{24}N_4$: M^+H = 237.

^{1}H NMR (D$_2$O): δ 1.05-1.10 (m, 3H), 1.14- 2.85 (m, 13H), 3.08 - 4.03 (m, 5H).

Example 305

(±) cis-5-imino-3-methyl-N-(phenylmethyl)pyrrolidine-2-ethanamine, dihydrochloride
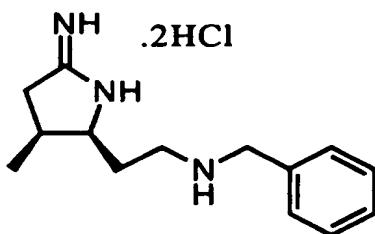
The title material is prepared in the same manner as described in Example 300 starting with the product of Example 300 C.

Example 306

(±) *trans*-5-imino-N-(phenylmethyl)-3-(trifluoromethyl)pyrrolidine-2-ethanamine, dihydrochloride
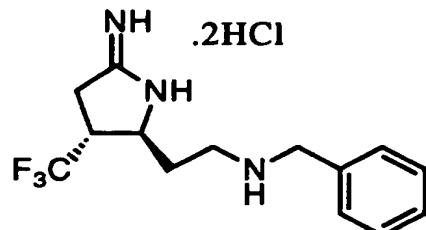
The title material is prepared in the same manner as described in Example 300 starting with Example 223 B.

Example 307

(±) *cis*-5-imino-N-(phenylmethyl)-3-(trifluoromethyl)pyrrolidine-2-ethanamine, dihydrochloride
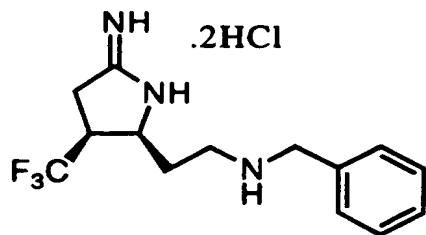
The title material is prepared in the same manner as described in Example 300 starting with Example 223 B.

Example 308

(±) *trans*-5-imino-3-methyl-N-[(2-thienyl)methyl]pyrrolidine-2-ethanamine, dihydrochloride
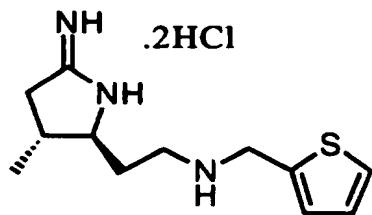
The title material is prepared in the same manner as described in Example 300 starting with Example 300 C.

Example 309

(±) *trans*-5-imino-N-[(2-thienyl)methyl]-3-(trifluoromethyl)-pyrrolidine-2-ethanamine, dihydrochloride
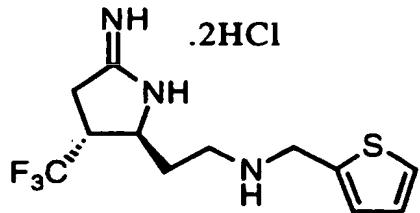
The title material is prepared in the same manner as described in Example 300 starting with Example 223 B.

Example 310

(±) *cis*-5-imino-3-methyl-N-[(2-thienyl)methyl]pyrrolidine-2-ethanamine, dihydrochloride
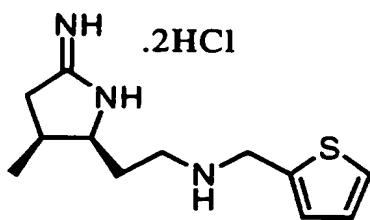
The title material is prepared in the same manner as described in Example 300 starting with Example 300 C.

Example 311

(±) *cis*-5-imino-N-[(2-thienyl)methyl]-3-(trifluoromethyl)-pyrrolidine-2-ethanamine, dihydrochloride
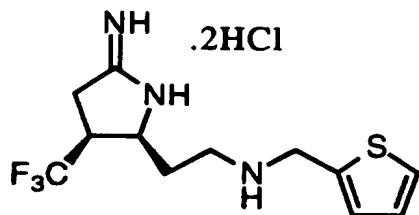
The title material is prepared in the same manner as described in Example 300 starting with Example 223 B.

Example 312

(±) *trans*-5-imino-3-methyl-α-phenylpyrrolidine-2-
ethanamine, dihydrochloride

5
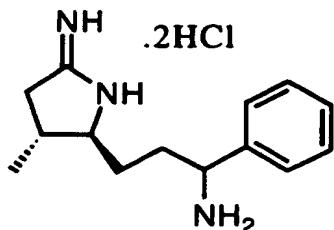
Example 312 A)   To a stirring solution of phenylnitromethane
and DBU in CH_3CN is added the product of Example 300 B.
10   After 16 h, the reaction is concentrated under vacuum. The
residue is partitioned between brine and EtOAc. The organic
layer is washed with brine, dried over Na_2SO_4, filtered and
stripped to obtain the nitroolefin.
Example 312 B)   The nitro amidine is prepared in the same
15   manner as described in Examples 300 E and 300 from Example
312 A.
Example 312)   A solution of the product of Example of 312 B
is reduced under catalytic hydrogenation conditions using Pd
black. The product is purified by reverse phase
20   chromatography on a C-18 column using a gradient of H_2O and
CH_3CN as the eluent.

Example 313

25

(±) *cis*-5-imino-3-methyl-α-phenylpyrrolidine-2-
ethanamine, dihydrochloride

30
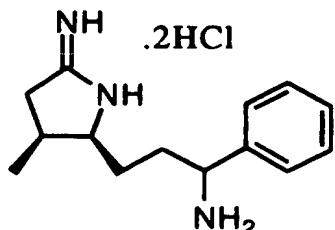
The title material is obtained from the reverse phase chromatography separation of Example 312.

Example 314

(±) *trans*-5-imino-3-methyl-N-(phenylmethyl)pyrrolidine-2-propanamine, dihydrochloride
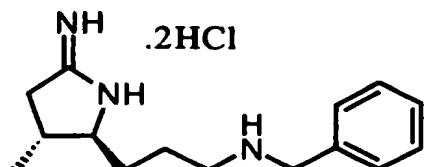
The title material is prepared in the same manner as described in Example 300 starting with *cis* and *trans*-5-[(1,3-dioxolan-2-yl)ethyl]-4-(methyl)pyrrolidin-2-one.

Example 315

(±) *cis*-5-imino-3-methyl-N-(phenylmethyl)pyrrolidine-2-propanamine, dihydrochloride
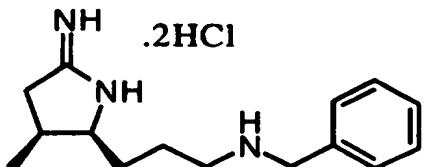
The title material is prepared in the same manner as described in Example 300 starting with *cis* and *trans*-5-[(1,3-dioxolan-2-yl)ethyl]-4-(methyl)pyrrolidin-2-one.

Example 316

(±) *trans*-5-imino-a,3-dimethyl-N-(phenylmethyl)pyrrolidine-2-propanamine, dihydrochloride
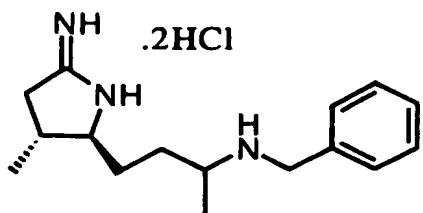
The title material is prepared in the same manner as
described in Example 300 starting with *cis* and *trans*-5-[2-
(1,3-dioxolan-2-yl)propyl]-4-(methyl)pyrrolidin-2-one.

Example 317

(±) *cis*-5-imino-a,3-dimethyl-N-(phenylmethyl)pyrrolidine-
2-propanamine, dihydrochloride
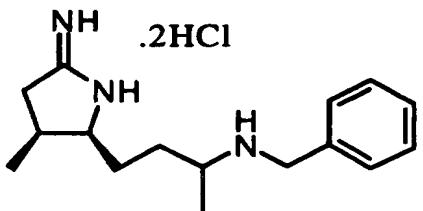
The title material is prepared in the same manner as
described in Example 300 starting with *cis* and *trans*-5-[2-
(1,3-dioxolan-2-yl)propyl]-4-(methyl)pyrrolidin-2-one.

Example 318

hexahydro-7-imino-α-[[(3,4-dihydro-2H-pyrrol-5-
yl)amino]methyl]-1H-azepine-2-acetamide,
bis(trifluoroacetate) salt
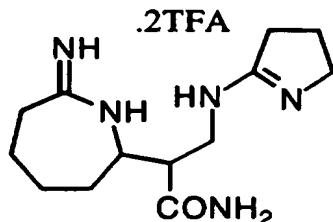
Example 318 A)   The 7-[1-methoxycarbonyl-2-
aminoethyl]homoiminopiperidine product of Example 281 D
5   is allowed to react with an ethanolic ammonia solution to
afford 7-[1-carboxamide-2-aminoethyl]homoiminopiperidine.
Example 318)   The 7-[1-carboxamide-2-
aminoethyl]homoiminopiperidine product of Example 318 A
is allowed to react with 2-methoxypyrroline by the method
10   of Example 236 to afford the title product.

Example 319

15   β-cyclopropylhexahydro-7-imino-1H-azepine-2-ethanamine,
bis(trifluoroacetate) salt
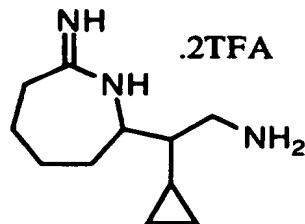
20   Example 319 A)   To cyclopropyl carboxaldehyde in MeOH is
added nitromethane and triethylamine. After stirring,
the solvent is removed in vacuo and the residue is
dissolved in CH_2Cl_2. The 2-nitro-1-cyclopropylethanol is
isolated from the methylene chloride solution and added
25   to a mixture of sodium acetate and acetic anhydride under
N_2. After stirring, the mixture is diluted with water
and extracted with EtOAc. The combined extracts are
washed with brine, dried over $MgSO_4$ and the solvent is
removed in vacuo. The 2-nitroethenylcyclopropane is used
30   without further purification.

Example 319 B) Reaction of the 2-nitroethenyl
cyclopropane product of Example 319 A with 1-morpholino-
1-cyclohexene followed by mild hydrolysis affords 2-[1-
cyclopropyl-2-nitroethyl]cyclohexanone.

5 Example 319 C) Beckmann Rearrangement of the 2-[1-
cyclopropyl-2-nitroethyl]cyclohexanone product of Example
319 B affords 7-[1-cyclopropyl-2-nitroethyl]caprolactam.
Example 319 D) The 7-[1-cyclopropyl-2-
nitroethyl]caprolactam product of Example 319 C is

10 converted to the corresponding amidine via the method of
Example 228 C to afford 7-[1-cyclopropyl-2-nitroethyl]
homoiminopiperidine.
Example 319) The 7-[1-cyclopropyl-2-nitroethyl]
homoiminopiperidine product of Example 319 D is dissolved

15 in acetic acid and reduced via catalytic hydrogenation as
described in the method of Example 205 to afford the
title product.

20   Example 320

hexahydro-7-imino-α-(1H-imidazol-5-yl)-1H-azepine-2-
ethanamine, bis(trifluoroacetate) salt

25
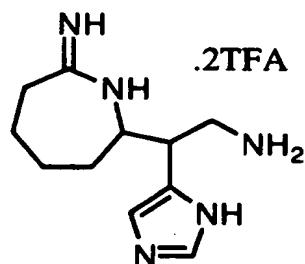
Example 320 A) To 2-imidazole carboxaldehyde in MeOH is
added nitromethane and triethylamine. After stirring,
the solvent is removed in vacuo and the residue is
30 dissolved in CH_2Cl_2. The 2-nitro-1-(2-imidazole)ethanol
is isolated from the methylene chloride solution and
added to a mixture of sodium acetate and acetic anhydride
under N_2. After stirring, the mixture is diluted with

water and extracted with EtOAc. The combined extracts are washed with brine, dried over MgSO$_4$ and the solvent is removed in vacuo. The 4-(2-nitroethenyl)imidazole product is used without further purification.

Example 320 B)   Reaction of the 4-(2-nitroethenyl)imidazole product of Example 320 A with 1-morpholino-1-cyclohexene followed by mild hydrolysis affords 2-[1-(4-imidazole)-2-nitroethyl]cyclohexanone. .

Example 320 C)   Beckmann Rearrangement of the 2-[1-(4-imidazole)-2-nitroethyl]cyclohexanone product of Example 320 B affords 7-[1-(4-imidazole)-2-nitroethyl]caprolactam.

Example 320 D)   The 7-[1-(4-imidazole)-2-nitroethyl]caprolactam product of Example 320 C is converted to the corresponding amidine via the method of Example 228 C to afford 7-[1-(4-imidazole)-2-nitroethyl]homoiminopiperidine.

Example 320)   The 7[1-(4-imidazole)-2-nitroethyl]homoiminopiperidine product of Example 320 D is dissolved in acetic acid and reduced via catalytic hydrogenation by the method of Example 205 to afford the title product.

Example 321

4-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]cyclohexanamine, dihydrochloride
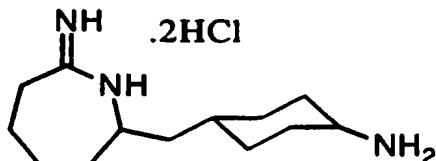
The product of Example 274 (0.31 g, 1.2 mmol) in 30 mL of EtOH was reduced with Rhodium on carbon under 60 psi of hydrogen at 60 °C. Solvent removal in vacuo followed by lyophilization in water gave 0.3 g of the title material.

Example 322

5   α-aminohexahydro-7-imino-β-phenyl-1H-azepine-2-propanoic
acid, dihydrochloride
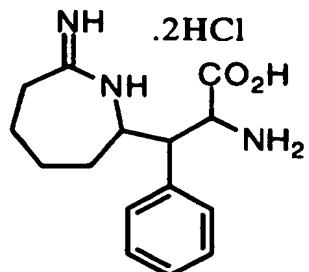
10   Example 322 A)   The product of Example 253 (2.4 g, 9
mmol) in 50 mL of CH_2Cl_2 was reacted with Et_3N (1.9 mL,
14 mmol) and TBDMSCl (1.5 g, 10 mmol) for 16 h at ambient
temperature under N_2. The reaction mixture was then
partitioned between water and Ch_2Cl_2. Drying (Na_2SO_4)

15   the organic layer followed by solvent removal gave 3.3 g
(98%) of the desired silylated lactam.
Example 322 B)   The product of Example 322 A (2.3 g, 6.0
mmol) in 80 mL of anhydrous THF was reacted with LiHMDS
(9.6 mL, 9.6 mmol) at -75 ^0C under N_2. Gradual warming

20   (45 min) to -30 ^0C was followed by addition of
methylchloroformate (1.0 g, 11 mmol) after which the
reaction mixture was stirred for an hour between -30 to
-20 ^0C. Quenching with 20 mL of 4N HCl in dioxane was
followed by extraction with water. Drying (Na_2SO_4) the

25   organic layer, solvent removal and chromatographic
purification (silica: 100% EA) gave 1.24 g (64%) of the
desired 7-(2-carbomethoxy-2-nitro-1-
phenylethyl)caprolactam.

30   Elemental analysis: $C_{16}H_{20}N_2O_5$. 0.8 H_2O (MW = 334.75).

	C	H	N
Calculated:	57.41	6.50	8.37
Found:	57.34	6.11	8.01

Example 322 C)   The product of Example 322 B (1.1 g, 3.6
mmol) dissolved in 50 mL of CH2Cl2 was treated with
Me3O+BF4- (0.6 g, 4.3 mmol) by the method of Example 3 to
5   give 850 mgs of its imino ether.

Example 322 D)   The product of Example 322 C (0.85 g, 2.5
mmol) in 50 mL of EtOH was refluxed with NH4Cl (0.13 g,
2.5 mmol) by the method of Example 4 to give its amidine
hydrochloride.

10   Example 322 E)   The crude product of Example 322 D in
AcOH was treated with 20% palladium black under 5 psi
hydrogen by the method of Example 205 to reduce the nitro
group. The crude mixture was then stripped of solvent in
vacuo, redissolved in 2N HCl and refluxed for 3 hours

15   under N2 in order to hydrolyze the ester group.
Chromatographic purification gave the title material.

Example 323

20

α-aminohexahydro-7-imino-β-(2-thienyl)-1H-azepine-2-
propanoic acid, dihydrochloride
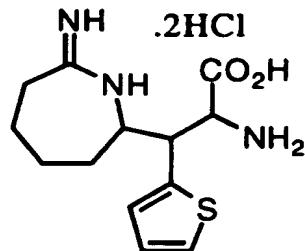
25

Example 323 A)   The nitro lactam precursor to the title
product of Example 262 is treated with TBDMSCl (1.1 eq)
and Et3N (1.5 eq) by the method of Example 322 A to give
the desired silylated lactam.

30   Example 323 B)   The product of Example 323 A is converted
to the desired 7-(2-carbomethoxy-2-nitro-1-
thiophenylethyl)caprolactam following the method of
Example 322 B

Example 323 C)   The product of Example 323 B in CH2Cl2 is treated with Me3O+BF4- (1.0 eq) by the method of Example 3 to give its imino ether.

Example 323 D)   The product of Example 323 C in EtOH is
5   refluxed with NH4Cl (1.1 eq) by the method of Example 4 to give its amidine hydrochloride.

Example 323)   The crude product of Example 323 D in AcOH is treated with 20% palladium black under 5 psi hydrogen by the method of Example 205 to reduce the nitro group.
10   The crude mixture is then stripped of solvent in vacuo, redissolved in 2N HCl and refluxed for 3 hours under N2 in order to hydrolyze the ester group. Chromatographic purification gives the title material

15

Example 324

α-(aminomethyl)hexahydro-7-imino-1H-azepine-2-
acetonitrile, bis(trifluoroacetate) salt
20
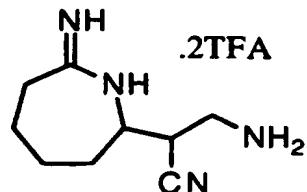
Example 324 A)   A sample of the 7-[1-methoxycarbonyl-2-nitroethyl]caprolactam product of Example 281 C is
25   allowed to react with ethanolic ammonia to afford 7-[1-carboxamide-2-nitroethyl]caprolactam.

Example 324 B)   The 7-[1-carboxamide-2-nitroethyl]caprolactam product of Example 324 A is reduced via catalytic hydrogenation to afford 7-[1-
30   carboxamide-2-aminoethyl]caprolactam.

Example 324 C)   The 7-[1-carboxamide-2-aminoethyl]caprolactam product of Example 324 B is protected with an Fmoc protecting group on the primary amino group to afford 7-[1-carboxamide-2-(Fmoc-
35   amino)ethyl]caprolactam.

Example 324 D)   The 7-[1-carboxamide-2-(Fmoc-amino)ethyl]caprolactam product of Example 324 C is allowed to react with trifluoroacetic anhydride and pyridine to afford after mild hydrolysis, 7-[1-cyano-2-
5   (Fmoc-amino)ethyl]caprolactam
Example 324 E)   The 7-[1-carboxamide-2-(Fmoc-amino)ethyl]caprolactam product of Example 324 D is converted to the corresponding amidine via the method of Example 228 C to afford 7-[1-cyano-2-(Fmoc-
10   amino)ethyl]homoiminopiperidine.
Example 324 F)   The Deprotection of 7-[1-cyano-2-(Fmoc-amino)ethyl]homoiminopiperidine product of Example 324 E with diethylamine affords 7-[1-cyano-2-aminoethyl]homoiminopiperidine.
15   Example 324)   The 7-[1-cyano-2-aminoethyl]homoiminopiperidine product of Example 324 F is allowed to react with 2-methoxypyrroline by the method of Example 236 to afford the title product.

20   The following Examples are prepared via suitable modifications of applicable methods described within this application.

Example 325

25

5-imino-3-methylene-N-(phenylmethyl)pyrrolidine-2S-ethanamine, dihydrochloride
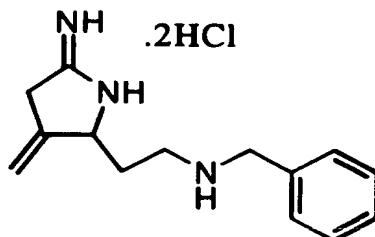
Example 326

β-ethynylhexahydro-7-imino-N-(3,4-dihydro-2H-pyrrol-5-
5   yl)-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt

10   Example 327

hexahydro-β-(1H-imidazol-1-yl)-7-imino-N-(3,4-dihydro-2H-
pyrrol-5-yl)-1H-azepine-2-ethanamine,
bis(trifluoroacetate) salt

15

Example 328

20
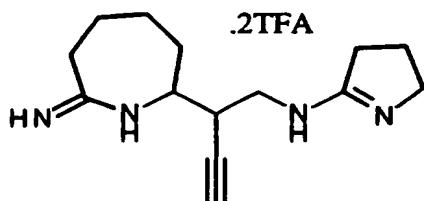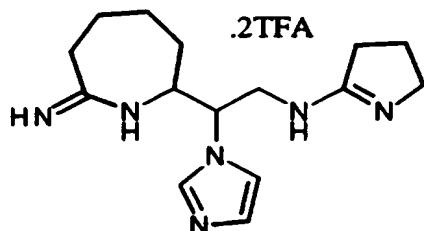
3-[[2-(hexahydro-7-imino-1H-azepin-2-yl)-2-(2-
thienyl)ethyl]amino]alanine, trihydrochloride
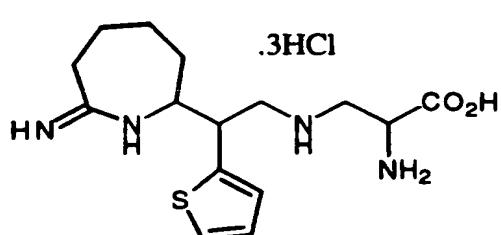
Biological Data

The activity of the above listed compounds as NO synthase inhibitors has been determined in the following assays:

Citrulline Assay for Nitric Oxide Synthase

Nitric oxide synthase (NOS) activity was measured by monitoring the conversion of [3H]-arginine to [3H]-citrulline (Bredt and Snyder, Proc. Natl. Acad. Sci. U.S.A., 87, 682-685, 1990 and Misko et al, Eur. J. Pharm., 233, 119-125, 1993). Human inducible NOS (hiNOS), human endothelial constitutive NOS (hecNOS) and human neuronal constitutive NOS (hncNOS) were each cloned from RNA extracted from human tissue. The cDNA for human inducible NOS (hiNOS) was isolated from a λcDNA library made from RNA extracted from a colon sample from a patient with ulcerative colitis. The cDNA for human endothelial constitutive NOS (hecNOS) was isolated from a λcDNA library made from RNA extracted from human umbilical vein endothelial cells (HUVEC) and the cDNA for human neuronal constitutive NOS (hncNOS) was isolated from a λcDNA library made from RNA extracted from human cerebellum obtained from a cadaver. The recombinant enzymes were expressed in Sf9 insect cells using a baculovirus vector (Rodi et al, in The Biology of Nitric Oxide, Pt. 4: Enzymology, Biochemistry and Immunology; Moncada, S., Feelisch, M., Busse, R., Higgs, E., Eds.; Portland Press Ltd.: London, 1995; pp 447-450). Enzyme activity was isolated from soluble cell extracts and partially purified by DEAE-Sepharose chromatography. To measure NOS activity, 10 μL of enzyme was added to 40 μL of 50 mM Tris (pH 7.6) in the presence or absence of test compounds and the reaction initiated by the addition of 50 μL of a reaction mixture containing 50mM Tris (pH 7.6), 2.0 mg/mL bovine serum albumin, 2.0 mM DTT, 4.0 mM CaCl2, 20 μM FAD, 100 μM tetrahydrobiopterin, 0.4-2.0 mM

NADPH and 60 μM L-arginine containing 0.9 μCi of L-[2,3-
^{3}H]-arginine. The final concentration of L-arginine in
the assay was 30 μM. For hecNOS, and hncNOS, calmodulin
was included at a final concentration of 40-100 nM.

5 Following incubation at 37° C for 15 minutes, the
reaction was terminated by addition of 300 μL of cold
stop buffer containing 10 mM EGTA, 100 mM HEPES, pH 5.5
and 1 mM citrulline. [3H]-Citrulline was separated by
chromatography on Dowex 50W X-8 cation exchange resin and
10 radioactivity determined with a liquid scintillation
counter. Results are reported in Table I as the IC$_{50}$
values of compounds for hiNOS, hecNOS and hncNOS.
Compounds giving less than 50% inhibition at 100 μM were
reported as having IC$_{50}$ values of >100 μM and compounds
15 giving greater than 50% inhibition at 100 μM were
reported as having IC$_{50}$ values of <100 μM.

RAW cell nitrite assay

RAW 264.7 cells are plated to confluency on a 96-well
20 tissue culture plate grown overnight (17h) in the
presence of LPS to induce NOS. A row of 3-6 wells were
left untreated and served as controls for subtraction of
nonspecific background. The media was removed from each
well and the cells are washed twice with Krebs-Ringers-
25 Hepes (25mM, pH 7.4) with 2 mg/ml glucose. The cells are
then placed on ice and incubated with 50 μL of buffer
containing L-arginine (30 μM) +/- inhibitors for 1h. The
assay is initiated by warming the plate to 37°C in a
water bath for 1-2 h. Production of nitrite by
30 intracellular iNOS is linear with time. To terminate the
cellular assay, the plate of cells is placed on ice and
the nitrite-containing buffer removed and analyzed for
nitrite (Misko et al, Anal. Biochem., 214, 11-16, 1993).
All values are the average of triplicate wells and are
35 compared to a background-subtracted induced set of cells
(100% value). IC$_{50}$ values of compounds with RAW cell
mouse inducible NOS are reported in Table I.

The following examples were assayed with the
following results.

Table I

Compounds giving less than 50% inhibition at 100 µM
were reported as having IC_{50} values of >100 µM and
compounds giving greater than 50% inhibition at 100
µM were reported as having IC_{50} values of <100 µM.

| | $IC_{50}[\mu M]$ | | | |
Example Number	hiNOS	hecNOS	hncNOS	RAWcell
5	6.2	792	15	66
9	9.7	575	74	>100
14	62	651	30	170
16	3.6	599	14	1.8
21	4.3	147	7.8	58
34	8.1	183	24	
37	19	836	118	80
64	3	458	8.3	5.4
94	8.6	40	0.71	7.9
95	5.9	375	28	
191	9.3	1620	95	45
205	<100	>100	>100	
219A	<100	>100	<100	
220A	<100	>100	<100	
220B	<100	>100	<100	
221	>100	>100	>100	
222	>100	>100	>100	
227	<100	>100	<100	
228	>100	>100	<100	

$IC_{50}[\mu M]$

Example Number	hiNOS	hecNOS	hncNOS	RAWcell
229	>100	>100	>100	
230	>100	>100	>100	
231	>100	>100	>100	
232	>100	>100	>100	
233	>100	>100	>100	
234	<100	>100	>100	
235	<100	>100	<100	
236	<100	<100	<100	
237	<100	<100	<100	
238	<100	<100	<100	
239	<100	>100	<100	
240	<100	>100	>100	
241	<100	>100	<100	
242	<100	>100	<100	
243	<100	>100	<100	
244	<100	>100	<100	
245	<100	>100	<100	
246	<100	>100	<100	
247	<100	<100	<100	
248	<100	>100	<100	
249	<100	>100	<100	
250	<100	>100	<100	
251	<100	>100	>100	
252	<100	>100	<100	
253	>100	>100	>100	

$$IC_{50}[\mu M]$$

Example Number	hiNOS	hecNOS	hncNOS	RAWcell
254	<100	>100	>100	
255	<100	>100	>100	
256	>100	>100	>100	
257	>100	>100	>100	
258	<100	>100	>100	
259	<100	>100	>100	
260	>100	>100	>100	
261	<100	>100	<100	
262	<100	>100	>100	
263	<100	>100	<100	
264	<100	>100	<100	
265	<100	<100	<100	
266	<100	>100	>100	
267	<100	>100	<100	
268	>100	>100	>100	
269	<100	>100	>100	
270	<100	>100	<100	
271	<100	>100	<100	
272	<100	>100	<100	
273	<100	>100	<100	
274	<100	>100	<100	
275	>100	>100	<100	
276	<100	>100	<100	
277	<100	>100	<100	
278	<100	>100	<100	

$IC_{50}[\mu M]$

Example Number	hiNOS	hecNOS	hncNOS	RAWcell
279	<100	>100	<100	
280	<100	100	<100	
282	<100	<100	<100	
283	<100	>100	<100	
283A	<100	>100	<100	
283B	<100	>100	<100	
284	<100	<100	<100	
285	<100	<100	<100	
286	<100	>100	<100	
287	<100	>100	<100	
288	<100	>100	>100	
289	<100	>100	<100	
290	<100	>100	>100	
291	<100	>100	>100	
292	<100	>100	<100	
293	<100	>100	<100	
294	<100	<100	<100	
295	<100	>100	<100	
296	>100	>100	>100	
297	>100	>100	>100	
298	<100	<100	<100	
299	<100	>100	<100	
300	<100	>100	<100	
301	<100	<100	<100	
302	<100	>100	<100	

$IC_{50}[\mu M]$

Example Number	hiNOS	hecNOS	hncNOS	RAWcell
303	<100	<100	<100	
304	<100	>100	<100	

In Vivo Assay

Rats were treated with an intraperitoneal injection of 10-12.5 mg/kg of endotoxin (LPS) to induce systemic expression of inducible nitric oxide synthase, resulting in markedly elevated plasma nitrite/nitrate levels. Compounds were administered orally 1 hour prior to LPS administration and plasma nitrite/nitrate levels were determined 5 hours following LPS administration. As shown in Table II, both compounds inhibited the LPS induced increase in plasma nitrite/nitrate levels demonstrating the ability to inhibit inducible nitric oxide synthase activity in vivo.

TABLE II

% inhibition of plasma nitrite/nitrate levels in LPS treated rats

Example Number	% Inhibiton (10 mg/kg, p.o.)
64	35
5	37

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit

and scope thereof, can make various changes and
modifications of the invention to adapt it to various
usages and conditions.

What is claimed:

5   1.   A compound having the formula:
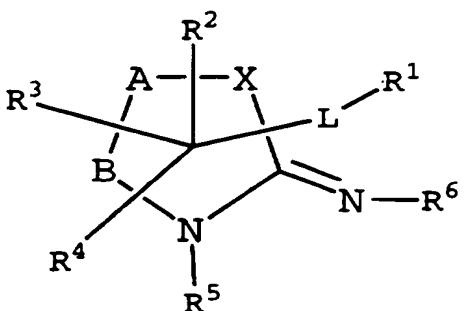
10

R^1 is selected from the group consisting of cycloalkyl,
heterocyclyl, and aryl, which may optionally be substituted
by one or more of the following: lower alkyl, lower alkenyl,
lower alkynyl, hydroxy, lower alkoxy, thiol, lower
15   thioalkoxy, $S(O)R^9$, $S(O)_2R^9$, halogen, nitro, amino,
alkylamino, dialkylamino, aminoalkyl, dialkylaminoalkyl,
arylamino, aminoaryl, alkylaminoaryl, acylamino, amidino,
carboxyl, carboalkoxy, carboaryloxy, carboarylalkyloxy,
cyano, aminocarbonylalkoxy, aminocarbonylamino,
20   aminocarbonylaminoalkyl, haloalkyl, $SO_2NR^7R^9$, wherein all
said substitutions may be optionally substituted with one or
more of the following: halogen, lower alkyl, amino,
alkylamino, dialkylamino, aminoalkyl, aminoacyl, carboxyl,
carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower
25   alkoxy;

L is selected from the group consisting of lower
alkylene, lower alkenylene, lower alkynylene, and
$-(CH_2)_m-D-(CH_2)_n-$;

30

D is selected from the group consisting of O, S, SO, SO$_2$, SO$_2$NR^7, NR^{7}SO$_2$, NR^8, POOR^7, PON(R^7)$_2$, POOR^{7}NR^7, NR^{7}POOR^7, C(O), C(O)O;

R^7 is hydrogen, lower alkyl, or aryl;

R^8 is hydrogen, lower alkyl, COR^9, or CO$_2$R^9;

R^9 is lower alkyl, or aryl;

m = 0 to about 7;

n = 0 to about 5;

wherein L may optionally be substituted by one or more of the following: lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, S(O)R^9, S(O)$_2$R^9, halogen, nitro, amino, alkylamino, dialkylamino, aminoalkyl, dialkylaminoalkyl, arylamino, aminoaryl, alkylaminoaryl, acylamino, carboxyl, carboalkoxy, carboaryloxy, carboarylalkyloxy, cyano, aminocarbonylalkoxy, aminocarbonylamino, aminocarbonylaminoalkyl, haloalkyl, SO$_2$NR^{7}R^9, cycloalkyl, heterocyclyl, aryl, heteroaryl, lactonyl, lactamyl, amidino, isourea, isothiourea, guanidino, substituted guanidino, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, amino, alkylamino, dialkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy, nitro, amidino, guanidino, substituted guanidino, isourea, isothiourea and

X is selected from the group consisting of NH, O, S, (CH$_2$)$_p$, and CH=CH;

p = 0 to about 4;

A is selected from the group consisting of O, NR^7, (CH$_2$)$_q$, CH=CH;

q = 1 to about 2;

5

B is selected from the group consisting of (CH$_2$)$_v$, CH=CH;

v = 1 to about 2;

10   R^2, R^3, and R^4 are independently selected from hydrogen, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, S(O)R^9, S(O)$_2$R^9, halogen, nitro, amino, alkylamino, dialkylamino, aminoalkyl, dialkylaminoalkyl, arylamino, aminoaryl,

15   alkylaminoaryl, acylamino, carboxyl, carboalkoxy, carboaryloxy, carboarylalkyloxy, cyano, aminocarbonylalkoxy, aminocarbonylamino, aminocarbonylaminoalkyl, haloalkyl, SO$_2$NR^{7}R^9, wherein all said substitutions may be optionally substituted with one

20   or more of the following: halogen, lower alkyl, amino, alkylamino, dialkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy, and

25   and R^2, R^3, may optionally be taken together to form an exocyclic double bond, alicyclic hydrocarbon, heterocyclyl or aromatic hydrocarbon and said optionally formed unit may be optionally substituted with one or more of the following:

30

lower alkyl, lower alkenyl, lower alkynyl which may be optionally substituted with carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy; and

35   R^5, R^6 are independently selected from the group consisting of hydrogen, hydroxy, and alkyloxy.

2.   The compound as recited in Claim 1 wherein:

R^1 is selected from the group consisting of cycloalkyl, heterocyclyl, and aryl, which may optionally be substituted by one or more of lower alkyl, lower alkenyl, lower alkynyl,

5 hydroxy, lower alkoxy, thiol, lower thioalkoxy, $S(O)R^9$, $S(O)_2R^9$, amino, amidino, alkylamino, aminoalkyl, aminoaryl, carboxyl, carboalkoxy, carboaryloxy, aminocarbonylalkoxy, aminocarbonylamino, $SO_2NR^7R^9$, wherein all said substitutions may be optionally substituted with one or more of the

10 following: lower alkyl, amino, alkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy, and

L is selected from the group consisting of lower

15 alkylene, lower alkenylene, lower alkynylene, and $-(CH_2)_m-D-(CH_2)_n-$;

D is O, S, SO, SO_2, NR^8, C(O), C(O)O or $POOR^7$;

20 R^7 is hydrogen, lower alkyl, or aryl;

R^8 is hydrogen, lower alkyl, COR^9, or CO_2R^9;

R^9 is lower alkyl, or aryl;

25

m = 0 to about 4;

n = 0 to about 3;

30 wherein L may optionally be substituted by one or more of lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, $S(O)R^9$, $S(O)_2R^9$, amino, alkylamino, aminoalkyl, arylamino, aminoaryl, carboxyl, carboalkoxy, carboaryloxy, aminocarbonylalkoxy,

35 aminocarbonylamino, $SO_2NR^7R^9$, cycloalkyl, heterocyclyl, aryl, heteroaryl, lactonyl, amidino, isourea, isothiourea, guanidino, substituted guanidino wherein all said substitutions may be optionally substituted with one

or more of the following: lower alkyl, amino, alkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy, nitro,amidino, guanidino, substituted guanidino, isourea,
5   isothiourea, and

X is selected from the group consisting of NH, O, S, $(CH_2)_p$, or CH=CH;

10   p = 0 to about 3;

A is selected from the group consisting of O, NR^7, $(CH_2)_q$, CH=CH;

15   q = 1 to about 2;

B = is selected from the group consisting of $(CH_2)_v$, CH=CH;

20   v = 1 to about 2;

R^2, R^3, and R^4 are independently selected from hydrogen, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, $S(O)R^9$, $S(O)_2R^9$, amino,
25   alkylamino, aminoalkyl, arylamino, aminoaryl, carboxyl, carboalkoxy, carboaryloxy, aminocarbonylalkoxy, aminocarbonylamino, $SO_2NR^7R^9$, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, amino, alkylamino,
30   aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, and lower alkoxy and

and R^2, R^3, may optionally be taken together to form an
35   exocyclic double bond, alicyclic hydrocarbon, heterocyclyl or aromatic hydrocarbon;

R^5, R^6 are independently selected from the group
consisting of hydrogen, hydroxy, and alkyloxy;

3.   The compound as recited in Claim 1 wherein:

R^1 is selected from the group consisting of cycloalkyl,
heterocyclyl, and aryl, which may optionally be substituted
by one or more of lower alkyl, lower alkenyl, lower alkynyl,
hydroxy, lower alkoxy, thiol, lower thioalkoxy, S(O)R^9,
S(O)$_2$R^9, amino, aminoalkyl, aminoaryl, carboxyl,
carboalkoxy, carboaryloxy, aminocarbonylalkoxy,
aminocarbonylamino, SO$_2$NR^{7}R^9, wherein all said substitutions
may be optionally substituted with one or more of the
following: lower alkyl, amino, aminoalkyl, aminoacyl,
carboxyl, carboalkoxy, carboaryloxy, hydroxy, lower alkoxy,
and

L is selected from the group consisting of lower
alkylene, lower alkenylene, lower alkynylene, and
-(CH$_2$)$_m$-D-(CH$_2$)$_n$- ;

D is selected from the group consisting of O, S, SO, SO$_2$,
NR^8, C(O), C(O)O;

R^7 is H, lower alkyl, or aryl;

R^8 is H, lower alkyl, COR^9, or CO$_2$R^9;

R^9 is lower alkyl, or aryl;

m = 0 to about 4;

n = 0 to about 3;

wherin L may optionally be substituted by one or more of
lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower
alkoxy, thiol, lower thioalkoxy, S(O)R^9, S(O)$_2$R^9, amino,

aminoalkyl, aminoaryl, carboxyl, carboalkoxy, carboaryloxy, aminocarbonylalkoxy, aminocarbonylamino, $SO_2NR^7R^9$, cycloalkyl, heterocyclyl, aryl, heteroaryl, lactonyl, amidino, guanidino, substituted guanidino,

5 wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, amino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, hydroxy, lower alkoxy, nitro, amidino, guanidino, substituted guanidino;

10

X is selected from the group consisting of NH, O, S, $(CH_2)_p$, and CH=CH;

p = 0 to about 3;

15

A is selected from the group consisting of O, NR^7, $(CH_2)_q$, CH=CH;

q = 1 ;

20

B = is selected from the group consisting of $(CH_2)_v$, CH=CH;

v = 1 ;

25

R^2, R^3, and R^4 are independently selected from hydrogen, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, $S(O)R^9$, $S(O)_2R^9$, amino, aminoalkyl, aminoaryl, carboxyl, carboalkoxy,

30 carboaryloxy, aminocarbonylalkoxy, aminocarbonylamino, $SO_2NR^7R^9$, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, amino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, hydroxy, lower alkoxy, and

35

R^5, R^6 are independently selected from the group consisting of hydrogen, hydroxy, and alkyloxy.

4.   The compound as recited in Claim 1 wherein:

R^1 is selected from the group consisting of cycloalkyl,
heterocyclyl, and aryl, which may optionally be substituted
5   by one or more of lower alkyl, lower alkenyl, lower alkynyl,
hydroxy, lower alkoxy, thiol, lower thioalkoxy, amino,
aminoalkyl, aminoaryl, carboxyl, carboalkoxy, carboaryloxy,
aminocarbonylalkoxy, aminocarbonylamino, wherein all said
substitutions may be optionally substituted with one or more
10   of the following: lower alkyl, amino, aminoalkyl, aminoacyl,
carboxyl, carboalkoxy, carboaryloxy, hydroxy, lower alkoxy,
and

L is selected from the group consisting of lower
15   alkylene, lower alkenylene, lower alkynylene, which may
optionally be substituted by one or more of the
following: lower alkyl, lower alkenyl, lower alkynyl,
hydroxy, lower alkoxy, thiol, lower thioalkoxy, amino,
aminoalkyl, aminoaryl, carboxyl, carboalkoxy,
20   carboaryloxy, aminocarbonylalkoxy, aminocarbonylamino,
wherein all said substitutions may be optionally
substituted with one or more of the following: lower
alkyl, amino, aminoalkyl, aminoacyl, carboxyl,
carboalkoxy, carboaryloxy, hydroxy, lower alkoxy, nitro,
25   amidino, guanidino, substituted guanidino;

X is selected from the group consisting of NH, O, S,
$(CH_2)_p$, CH=CH;

30   p = 0 to about 3;

A is selected from the group consisting of CH_2, CH=CH;

B is selected from the group consisting of CH_2, CH=CH;
35

R^2, R^3, and R^4 are independently selected from hydrogen,
lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower
alkoxy, thiol, lower thioalkoxy, amino, aminoalkyl,

aminoaryl, carboxyl, carboalkoxy, carboaryloxy, aminocarbonylalkoxy, aminocarbonylamino, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, amino, aminoalkyl,

5   aminoacyl, carboxyl, carboalkoxy, carboaryloxy, hydroxy, lower alkoxy, and

R^5, R^6 are independently selected from the group consisting of hydrogen, hydroxy, and alkyloxy;

10

        5.   The compound as recited in Claim 1 wherein:

R^1 is selected from the group consisting of cycloalkyl, heterocyclyl, and aryl which may optionally be substituted

15   by one or more of lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, amino, aminoalkyl, aminoaryl, carboxyl, carboalkoxy, carboaryloxy wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, amino,

20   aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, hydroxy, lower alkoxy, and

L is selected from the group consisting of a linker group such as alkylene, alkenylene, alkynylene, which may

25   optionally be substituted by one or more of lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, amino, aminoalkyl, carboxyl, carboalkoxy, carboaryloxy wherein all said substitutions may be optionally substituted with one or more of the

30   following: lower alkyl, amino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, hydroxy, lower alkoxy, nitro, amidino, guanidino, substituted guanidino and

35   X is selected from the group consisting of $(CH_2)_p$, and $CH=CH$;

        $p = 0$ to 3;

A is selected from the group consisting of CH2, and CH=CH;

5   B is selected from the group consisting of CH2, and CH=CH;

R^2, R^3, and R^4 are independently selected from hydrogen, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower
10   alkoxy, thiol, lower thioalkoxy, amino, aminoalkyl, carboxyl, carboalkoxy, carboaryloxy wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, amino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, hydroxy,
15   and lower alkoxy; and

R^5, R^6 are independently selected from the group consisting of hydrogen, hydroxy, and alkyloxy.

20   6.   The compound as defined in Claim 1 wherein the compound is selected from the group consisting of

hexahydro-7-(phenylmethyl)-2H-azepin-2-imine, monohydrochloride;
25
hexahydro-3-(phenylmethyl)-2H-azepin-2-imine, monohydrochloride;

7-(cyclohexylmethyl)hexahydro-2H-azepin-2-imine,
30   monohydrochloride;

3-(cyclohexylmethyl)hexahydro-2H-azepin-2-imine, monohydrochloride;

35   (+)-hexahydro-7-(phenylmethyl)-2H-azepin-2-imine, monohydrochloride;

(-)-hexahydro-7-(phenylmethyl)-2H-azepin-2-imine,
monohydrochloride;

hexahydro-7-[(oxiran-2-yl)methyl]-2H-azepin-2-imine,
5   monohydrochloride;

7-[(1,4-benzodioxan-2-yl)methyl]hexahydro-2H-azepin-2-
imine, monohydrochloride;

10   hexahydro-7-[2-methoxy-3-(2-methoxyphenoxy)propyl]-2H-
azepin-2-imine, monohydrochloride;

hexahydro-a-[(2-hydroxyphenoxy)methyl]-7-imino-1H-
azepine-2-ethanol, monohydrochloride;
15
a-[(2-acetyloxyphenoxy)methyl]hexahydro-7-imino-1H-
azepine-2-ethanol acetate(ester), monohydrochloride;

hexahydro-7-(3-phenyl-2-propenyl)-2H-azepin-2-imine,
20   monohydrochloride;

hexahydro-7-(3-phenylpropyl)-2H-azepin-2-imine,
monohydrochloride;

25   hexahydro-7-[(tetrahydro-2-furanyl)methyl]-2H-azepin-2-
imine, monohydrochloride;

hexahydro-3-[(tetrahydro-2-furanyl)methyl]-2H-azepin-2-
imine, monohydrochloride;
30
7-[(2-furanyl)methyl]hexahydro-2H-azepin-2-imine,
monohydrochloride;

3-[(2-furanyl)methyl]hexahydro-2H-azepin-2-imine,
35   monohydrochloride;

hexahydro-7-[(2-thienyl)methyl]-2H-azepin-2-imine,
monohydrochloride;

hexahydro-3-[(2-thienyl)methyl]-2H-azepin-2-imine,
monohydrochloride;

5   (±)(trans) 4-methyl-5-(phenylmethyl)pyrrolidin-2-imine,
monohydrochloride;

octahydro-8-(3-phenyl-2-propenyl)azocin-2-imine,
monohydrochloride;
10
octahydro-8-(3-phenylpropyl)azocin-2-imine,
monohydrochloride;

methyl 2-[2-(hexahydro-7-imino-1H-azepin-2-
15   yl)ethenyl]benzoate, monohydrochloride;

methyl 2-[2-(hexahydro-7-imino-1H-azepin-2-
yl)ethyl]benzoate, monohydrochloride;

20   methyl 2-[2-(hexahydro-2-imino-1H-azepin-3-
yl)ethenyl]benzoate, monohydrochloride;

methyl 2-[2-(hexahydro-2-imino-1H-azepin-3-
yl)ethyl]benzoate, monohydrochloride;
25
methyl 3-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethenyl]
benzeneacetate, monohydrochloride;

6-(phenylmethyl)piperidin-2-imine, monohydrochloride;
30
6-(cyclohexylmethyl)piperidin-2-imine, monohydrochloride;

6-(3-phenyl-2-propenyl)piperidin-2-imine,
monohydrochloride;

35
6-(3-phenylpropyl)piperidin-2-imine, monohydrochloride;

7-[2-(1,3-dioxolan-2-yl)ethyl]hexahydro-2H-azepin-2-imine, monohydrochloride;

5   7-[2-(1,3-dioxan-2-yl)ethyl]hexahydro-2H-azepin-2-imine, monohydrochloride;

7-[[4,5-dihydro-3-(trifluoromethyl)isoxazol-5-yl]methyl]hexahydro-2H-azepin-2-imine, monohydrochloride;

10   7-[[4,5-dihydro-3-(trifluoromethyl)isoxazol-4-yl]methyl]hexahydro-2H-azepin-2-imine, monohydrochloride;

hexahydro-7-[[3-(trifluoromethyl)isoxazol-5-yl]methyl]-2H-azepin-2-imine, monohydrochloride;

15

hexahydro-7-[[3-(trifluoromethyl)isoxazol-4-yl]methyl]-2H-azepin-2-imine, monohydrochloride;

hexahydro-7-[(3-phenylisoxazol-4-yl)methyl]-2H-azepin-2-
20   imine, monohydrochloride;

hexahydro-7-[(3-phenylisoxazol-5-yl)methyl]-2H-azepin-2-imine, monohydrochloride;

25   7-[[4,5-dihydro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl]-hexahydro-2H-azepin-2-imine, monohydrochloride;

7-[[4,5-dihydro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-
30   4-yl]methyl]hexahydro-2H-azepin-2-imine, monohydrochloride;

hexahydro-7-[[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl]-2H-azepin-2-imine, monohydrochloride;

35

hexahydro-7-[[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl]-2H-azepin-2-imine, monohydrochloride;

7-[(4,5-dihydro-1,3-diphenyl-1H-pyrazol-4-
yl)methyl]hexahydro-2H-azepin-2-imine, monohydrochloride;

7-[(1,3-diphenyl-1H-pyrazol-5-yl)methyl]hexahydro-2H-
azepin-2-imine, monohydrochloride;

hexahydro-7-[[1-phenyl-3-(trifluoromethyl)-1H-1,2,4-
triazol-5-yl]methyl]-2H-azepin-2-imine,
monohydrochloride;

hexahydro-7-[2-(2-nitrophenyl)ethenyl]-2H-azepin-2-imine,
monohydrochloride;

2-[2-(hexahydro-7-imino-2H-azepin-2-yl)ethyl]benzenamine,
dihydrochloride;

methyl 2-[3-(hexahydro-7-imino-1H-azepin-2-yl)-1-
propenyl]-5-nitrobenzoate, monohydrochloride;

methyl 5-amino-2-[3-(hexahydro-7-imino-1H-azepin-2-yl)-1-
propenyl]benzoate, dihydrochloride;

hexahydro-7-[2-(3-methoxyphenyl)ethenyl]-2H-azepin-2-
imine, monohydrochloride;

hexahydro-7-[2-(3-methoxyphenyl)ethyl]-2H-azepin-2-imine,
monohydrochloride;

7-[2-(3-furanyl)ethyl]hexahydro-2H-azepin-2-imine,
monohydrochloride;

hexahydro-7-[2-(2-thienyl)ethenyl]-2H-azepin-2-imine,
monohydrochloride;

hexahydro-7-[2-(2-thienyl)ethyl]-2H-azepin-2-imine,
monohydrochloride;

methyl 5-[3-(hexahydro-7-imino-1H-azepin-2-yl)-1-propenyl]furan-2-carboxylate, monohydrochloride;

methyl 5-[3-(hexahydro-7-imino-1H-azepin-2-yl)propyl]furan-2-carboxylate, monohydrochloride;

hexahydro-7-[2-(2-thiazolyl)ethenyl]-2H-azepin-2-imine, monohydrochloride;

hexahydro-7-[2-(2-thiazolyl)ethyl]-2H-azepin-2-imine, monohydrochloride;

1,5,6,7-tetrahydro-7-(phenylmethyl)-2H-azepin-2-imine, monohydrochloride;

7-[(4,5-dihydro-3-phenylisoxazolyl-5-yl)methyl]hexahydro-2H-azepine-2-imine, monotrifluoroacetic acid salt;

7-[(2,6-dichlorophenyl)methyl]-hexahydro-2H-azepin-2-imine;

7-[(4-fluorophenyl)methyl]hexa-hydro-2H-azepin-2-imine;

7-[(4-fluorophenyl)methyl]hexa-hydro-2H-azepin-2-imine;

7-[(2,4-difluorophenyl)methyl]-hexahydro-2H-azepin-2-imine;

7-[(2,3,4,5-pentafluorophenyl)-methyl]hexahydro-2H-azepin-2-imine;

hexahydro-7-[[4-(trifluoro-methyl)phenyl]methyl]-2H-azepin-2-imine;

hexahydro-7-[[3-(trifluoro-methyl)phenyl]methyl]-2H-azepin-2-imine;

7-[(2-biphenylyl)methyl]hexa-hydro-2H-azepin-2-imine;

hexahydro-7-[(2-nitrophenyl)-methyl]-2H-azepin-2-imine;

hexahydro-7-[(4-nitrophenyl)-methyl]-2H-azepin-2-imine;

4-[(hexahydro-7-imino-2H-azepin-2-yl)methyl]benzene-
acetic acid;

7-[(5-chlorothien-2-yl)methyl]-hexahydro-2H-azepin-2-
imine;

7-[(3,5-dimethylisoxazol-4-yl)methyl]hexahydro-2H-azepin-
2-imine;

hexahydro-7-[(tetrahydro-2H-pyran-2-yl)methyl]-1H-azepin-
2-imine monohydrochloride;

hexahydro-3-[(tetrahydro-2H-pyran-2-yl)methyl]-2H-azepin-
2-imine;

hexahydro-7-(2-phenylethyl)-1H-azepin-2-imine,
monohydrochloride;

hexahydro-7-[2-(4-nitrophenyl)ethyl]-1H-azepin-2-imine,
monohydrochloride;

hexahydro-7-[2-(4-methoxyphenyl) ethyl]-1H-azepin-2-
imine, monohydrochloride;

7-[3-[5-(1,3-dioxolan-2-yl)thien-2-yl)-2-
propenyl]hexahydro-2H-azepin-2-imine, monohydrochloride;

5-[3-(hexahydro-7-imino-1H-azepin-2-yl)-1-
propenyl]thiophene-2-carboxamide, monohydrochloride;

methyl 2-[3-(hexahydro-7-imino-1H-azepin-2-yl)-1-
propenyl]-5-methoxybenzoate, monohydrochloride;

methyl hexahydro-7-imino-b-(4-methylphenyl)-1H-azepine-2-propanoate, monohydrochloride;

5   methyl hexahydro-2-imino-b-(4-methylphenyl)-1H-azepine-3-propanoate, monohydrochloride;

methyl 3-[4-(trifluoromethyl)phenyl]propenoate methyl hexahydro-7-imino-b-[4-(trifluoromethyl)phenyl]-1H-azepine-2-propanoate, monohydrochloride;

10

(2-nitroethenyl)benzene hexahydro-7-(2-nitro-1-phenylethyl)-2H-azepin-2-imine, monohydrochloride;

3-(2-furanyl)propenenitrile b-(2-furanyl)hexahydro-7-

15   imino-1H-azepine-2-propanenitrile, monohydrochloride;

methyl 3-(2-furanyl)propenoatemethyl β-(2-furanyl)hexahydro-7-imino-1H-azepine-2-propanoate, monohydrochloride;

20

(ethenylsulfonyl)benzene hexahydro-7-[2-(phenylsulfonyl)ethyl]-2H-azepin-2-imine, monohydrochloride;

25   hexahydro-7-imino-β-phenyl-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)-2-phenylethyl]methanesulfonamide, monohydrochloride;

30

γ-(2-furanyl)hexahydro-7-imino-1H-azepine-2-propanamine, dihydrochloride;

N-[3-(2-furanyl)-3-(hexahydro-7-imino-1H-azepin-2-

35   yl)propyl]methanesulfonamide, monohydrochloride;

methyl −β-(2,3-dihydroxypropyl)hexahydro-7-imino-1H-azepine-2-butanoate, monohydrochloride;

4-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]-3,4,5,6-
tetrahydro-6-hydroxy-2H-pyran-2-one, monohydrochloride;

5   hexahydro-7-[(4-morpholinyl)methyl]-2H-azepin-2-imine,
dihydrochloride;

hexahydro-2-imino-7-[(4-morpholinyl)methyl]-1H-azepin-3-
ol, dihydrochloride;
10
5-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]4,5-
dihydroisoxazol-3-amine, dihydrochloride;

5-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]-1-
15   methylpyrazolidin-3-one, dihydrochloride;

5-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]-1,2-dihydro-
3H-pyrazol-3-one, dihydrochloride;

20   (±)(cis) 4-methyl-5-(phenylmethyl)pyrrolidin-2-imine,
monohydrochloride;

(±)(trans) 4-methyl-5-(phenylmethyl)pyrrolidin-2-imine,
monohydrochloride;
25
(±)(cis) 5-(phenylmethyl)-4-(trifluoromethyl)pyrrolidin-
2-imine, monohydrochloride;

(±)(trans) 5-(phenylmethyl)-4-
30   (trifluoromethyl)pyrrolidin-2-imine, monohydrochloride;

4,4-dimethyl-5-(phenylmethyl)pyrrolidin-2-imine,
monohydrochloride;

35   5-(phenylmethyl)pyrrolidin-2-imine, monohydrochloride;

(±)(cis) 5-[(1,3-dioxolan-2-yl)methyl]-4-
(trifluoromethyl)pyrrolidin-2-imine, monohydrochloride;

(±)(*trans*) 5-[(1,3-dioxolan-2-yl)methyl]-4-
(trifluoromethyl)pyrrolidin-2-imine, monohydrochloride;

5   (±)(*trans*) 2-[2-hydroxy-3-[5-imino-3-
(trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
carboxylic acid, monohydrochloride;

(±)(*cis*) 2-[2-hydroxy-3-[5-imino-3-
10   (trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
carboxylic acid, monohydrochloride;

(±)ethyl (*trans*) 2-[3-[5-imino-3-
(trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
15   carboxylate, monohydrochloride;

(±)ethyl (*cis*) 2-[3-[5-imino-3-
(trifluoromethyl)pyrrolidin-2-yl]propyl]oxazole-4-
carboxylate, monohydrochloride;
20
(±)(*trans*) 2-[3-[5-imino-3-(trifluoromethyl)pyrrolidin-2-
yl]propyl]oxazole-4-carboxylic acid, monohydrochloride;

(±)(*cis*) 2-[3-[5-imino-3-(trifluoromethyl)pyrrolidin-2-
25   yl]propyl]oxazole-4-carboxylic acid, monohydrochloride;

(±)(*cis*) 5-[(4-methoxyphenyl)methyl]-3-methylpyrrolidin-
2-imine, monohydrochloride;

30   (±)(*trans*) 5-[(4-methoxyphenyl)methyl]-3-
methylpyrrolidin-2-imine, monohydrochloride;

hexahydro-3-[[(methoxyphenyl)methyl]thio]-2H-azepin-2-
imine, trifluoroacetate salt;
35
2-[2-(2-iminohexahydro-1H-azepin-3-yl)ethyl-1-
methylpyridinium chloride, monohydrochloride;

hexahydro-3-[2-(1-methylpiperidin-2-yl)ethyl]-2H-azepin-2-imine, dihydrochloride;

ethyl 5-[(hexahydro-2-imino-1H-azepin-3-yl)methyl]-4,5-
5   dihydroisoxazole-3-carboxylate, trifluoroacetate salt;

cyclohexyl hexahydro-7-iminoazepine-2-carboxylate, monohydrochloride;

10   phenylmethyl hexahydro-7-iminoazepine-2-carboxylate, monohydrochloride;

hexahydro-7-[3-(phenylmethoxy)propyl]-2H-azepin-2-imine, trifluoroacetate salt;
15
N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]benzenimidamide, bis(trifluoroacetate) salt;

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-3,4,5,6-
20   tetrahydro-2H-azepin-7-amine, bis(trifluoroacetate) salt;

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-2,3,4,5-tetrahydropyridin-6-amine, bis(trifluoroacetate) salt;

25   N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-3,4-dihydro-2H-pyrrol-5-amine, bis(trifluoroacetate) salt;

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]benzenesulfonamide, trifluoroacetate salt;
30
N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]benzenemethanesulfonamide, trifluoroacetate salt;

35   N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]morpholin-4-amine, bis(trifluoroacetate) salt;

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]pyridin-2-
methanamine, tris(trifluoroacetate) salt;

5   N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl] pyridin-3-
methanamine, tris(trifluoroacetate) salt;

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl] pyridin-4-
methanamine, tris(trifluoroacetate) salt;

10 1-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1H-
imidazole, bis(trifluoroacetate) salt;

1-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1H-1,2,4-
triazole, bis(trifluoroacetate) salt;

15

4-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-4H-1,2,4-
triazole, bis(trifluoroacetate) salt;

1-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1H-
20 tetrazole, trifluoroacetate salt;

methyl 1-[2-(hexahydro-7-imino-1H-azepin-2-
yl)ethyl]pyrrolidine-2-carboxylate,
bis(trifluoroacetate) salt;

25

4-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]morpholine,
bis(trifluoroacetate) salt;

1-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]piperazine,
30 bis(trifluoroacetate) salt;

1-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-4-
methylpiperazine, tris(trifluoroacetate) salt;

35 hexahydro-7-(2-nitro-1-phenyl)-2H-azepin-2-imine,
trifluoroacetate salt;

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)-2-phenylethyl]guanidine, bis(trifluoroacetate) salt;

hexahydro-N-(hexahydro-1H-azepin-2-ylidene)-7-imino-β-phenyl-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;

hexahydro-7-(2-nitro-1-phenylpropyl)-2H-azepin-2-imine, trifluoroacetate salt;

hexahydro-7-imino-α-methyl-β-phenyl-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;

hexahydro-7-imino-α-methyl-β-phenyl-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;

hexahydro-7-imino-α-methyl-β-cyclohexyl-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;

7-[1-(1,3-benzodioxol-5-yl)-2-nitropropyl]hexahydro-2H-azepin-2-imine, trifluoroacetate salt;

β-(1,3-benzodioxol-5-yl)hexahydro-7-imino-α-methyl-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;

hexahydro-7-[2-nitro-1-(2-thienyl)ethyl]-2H-azepine, trifluoroacetate salt;

hexahydro-7-imino-β-(2-thienyl)-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;

hexahydro-7-imino-β-(3-thienyl)-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;

hexahydro-7-imino-β-(2-furanyl)-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;

hexahydro-N-(hexahydro-1H-azepin-2-ylidene)-7-imino-β-
(2-thienyl)-1H-azepine-2-ethanamine,
bis(trifluoroacetate) salt;

5   hexahydro-7-imino-N-(2-pyrrolidinylidene)-β-(2-thienyl)-
1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;

hexahydro-7-[1-(1H-indol-3-yl)-2-nitroethyl]-2H-azepin-
2-imine, trifluoroacetate salt;

10
hexahydro-7-imino-β-(1H-indol-3-yl)-1H-azepine-2-
ethanamine, bis(trifluoroacetate) salt;

hexahydro-7-[(2-nitrophenyl)methyl]-2H-azepin-2-imine,
15   monohydrochloride;

2-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]benzenamine,
dihydrochloride;

20   2-[(hexahydro-7-imino-1H-azepin-2-
yl)methyl]cyclohexanamine, dihydrochloride;

hexahydro-7-[(4-nitrophenyl)methyl]-2H-azepin-2-imine,
monohydrochloride;
25
4-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]benzenamine,
dihydrochloride;

hexahydro-7-[[4-(trifluoromethyl)phenyl]methyl]-2H-
30   azepin-2-imine, monohydrochloride;

7-[(4-fluorophenyl)methyl]hexahydro-2H-azepin-2-imine,
monohydrochloride;

35   hexahydro-7-[[3-(trifluoromethyl)phenyl]methyl]-2H-
azepin-2-imine, monohydrochloride;

7-[(2,4-difluorophenyl)methyl]hexahydro-2H-azepin-2-imine, monohydrochloride;

7-[(2,6-dichlorophenyl)methyl]hexahydro-2H-azepin-2-imine, monohydrochloride;

hexahydro-7-[3-(2-thienyl)-2-propenyl]-2H-azepin-2-imine, monohydrochloride;

methyl α-[[[(3,4-dihydro-2H-pyrrol-5-yl)amino]methyl]hexahydro-7-imino-1H-azepine-2-acetate, bis(trifluoroacetate) salt;

4,5-dihydro-5-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]isoxazole-3-carboxylic acid, monohydrochloride;

ethyl 4,5-dihydro-5-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]isoxazole-3-carboxylate, trifluoroacetate salt;

4,5-dihydro-5-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]isoxazole-3-carboxamide, trifluoroacetate salt;

3-amino-5-[(hexahydro-7-imino-1H-azepine-2-yl0methyl]-tetrahydrofuran-2-one, bis(trifluoroacetate) salt;

7-[2-(2,2-dimethyldioxolan-4-yl)ethyl]hexahydro-2H-azepin-2-imine, monohydrochloride;

hexahydro-7-[2-(4-pyridinyl)ethyl]-2H-azepin-2-imine, monohydrochloride;

4-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]pyridinium-1-oxide, bis(trifluoroacetate) salt;

4-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1-
methylpyridinium chloride, monohydrochloride salt;

hexahydro-7-[2-(2-pyridinyl)ethyl]-2H-azepin-2-imine,
monohydrochloride;

2-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1-
methylpyridinium chloride, bis(trifluoroacetate) salt;

hexahydro-7-[2-(1-methylpiperidin-2-yl)ethyl]-2H-azepin-
2-imine, dihydrochloride;

hexahydro-7-[2-(2-piperidinyl)ethyl]-2H-azepin-2-imine,
dihydrochloride;

hexahydro-7-[2-(4-piperidinyl)ethyl]-2H-azepin-2-imine,
dihydrochloride;

hexahydro-7-[2-(4-piperidinyl)ethyl]-2H-azepin-2-imine,
dihydrochloride;

hexahydro-7-[2-[1-(methylsulfonyl)piperidin-2-yl]ethyl]-
2H-azepin-2-imine, trifluoroacetate salt;

3-(hexahydro-7-imino-1H-azepin-2-yl)-1-(4-
morpholinyl)propan-1-one, trifluoroacetate salt;

6-(phenylmethyl)piperidin-2-imine, monohydrochloride;

6-(cyclohexylmethyl)piperidin-2-imine,
monohydrochloride;

trans-N-[3-(5-imino-3-methylpyrrolidin-2-
yl)ethyl]phenylmethylamine, dihydrochloride;

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-4,5-
dihydro-1H-imidazol-2-amine, bis(trifluoroacetate) salt;

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1,4,5,6-
tetrahydropyrimidin-2-amine, bis(trifluoroacetate) salt;

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-3,4-
5   dihydro-4-methyl-2H-pyrrol-5-amine,
bis(trifluoroacetate) salt;

N-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-3,4-
dihydro-2-methyl-2H-pyrrol-5-amine,
10   bis(trifluoroacetate) salt;

(±) *cis*-5-imino-3-methyl-N-(phenylmethyl)pyrrolidine-2-
ethanamine, dihydrochloride;

15   (±) *trans*-5-imino-N-(phenylmethyl)-3-
(trifluoromethyl)pyrrolidine-2-ethanamine,
dihydrochloride;

(±) *cis*-5-imino-N-(phenylmethyl)-3-
20   (trifluoromethyl)pyrrolidine-2-ethanamine,
dihydrochloride;

(±) *trans*-5-imino-3-methyl-N-[(2-
thienyl)methyl]pyrrolidine-2-ethanamine,
25   dihydrochloride;

(±) *cis*-5-imino-N-[(2-thienyl)methyl]-3-
(trifluoromethyl)-pyrrolidine-2-ethanamine,
dihydrochloride;
30
(±) *cis*-5-imino-3-methyl-N-[(2-
thienyl)methyl]pyrrolidine-2-ethanamine,
dihydrochloride;

35   (±) *trans*-5-imino-N-[(2-thienyl)methyl]-3-
(trifluoromethyl)-pyrrolidine-2-ethanamine,
dihydrochloride;

(±) *trans*-5-imino-3-methyl-α-phenylpyrrolidine-2-ethanamine, dihydrochloride;

(±) *cis*-5-imino-3-methyl-α-phenylpyrrolidine-2-
5 ethanamine, dihydrochloride;

(±) *trans*-5-imino-3-methyl-N-(phenylmethyl)pyrrolidine-2-propanamine, dihydrochloride;

10 (±) *cis*-5-imino-3-methyl-N-(phenylmethyl)pyrrolidine-2-propanamine, dihydrochloride;

(±) *trans*-5-imino-a,3-dimethyl-N-(phenylmethyl)pyrrolidine-2-propanamine, dihydrochloride;
15
(±) *cis*-5-imino-a,3-dimethyl-N-(phenylmethyl)pyrrolidine-2-propanamine, dihydrochloride;

hexahydro-7-imino-α-[[(3,4-dihydro-2H-pyrrol-5-
20 yl)amino]methyl]-1H-azepine-2-acetamide,
bis(trifluoroacetate) salt;

β-cyclopropylhexahydro-7-imino-1H-azepine-2-ethanamine,
bis(trifluoroacetate) salt;
25
hexahydro-7-imino-α-(1H-imidazol-5-yl)-1H-azepine-2-
ethanamine, bis(trifluoroacetate) salt;

4-[(hexahydro-7-imino-1H-azepin-2-
30 yl)methyl]cyclohexanamine, dihydrochloride;

α-aminohexahydro-7-imino-β-phenyl-1H-azepine-2-propanoic
acid, dihydrochloride;

35 α-aminohexahydro-7-imino-β-(2-thienyl)-1H-azepine-2-
propanoic acid, dihydrochloride;

α-(aminomethyl)hexahydro-7-imino-1H-azepine-2-
acetonitrile, bis(trifluoroacetate) salt;

5-imino-3-methylene-N-(phenylmethyl)pyrrolidine-2S-
5   ethanamine, dihydrochloride;

β-ethynylhexahydro-7-imino-N-(3,4-dihydro-2H-pyrrol-5-
yl)-1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;

10   hexahydro-β-(1H-imidazol-1-yl)-7-imino-N-(3,4-dihydro-2H-
pyrrol-5-yl)-1H-azepine-2-ethanamine,
bis(trifluoroacetate) salt;

3-[[2-(hexahydro-7-imino-1H-azepin-2-yl)-2-(2-
15   thienyl)ethyl]amino]alanine, trihydrochloride.

7.   A method of inhibiting nitric oxide synthesis
in a subject in need of such inhibition by administering
a therapeutically effective amount of a compound of
20   claim 1,2,3,4,5 or 6.

8.   A method of selectively inhibiting nitric
oxide synthesis produced by inducible NO synthase over NO
produced by the constitutive forms of NO synthase in a
25   subject in need of such inhibition by administering a
therapeutically effective amount of a compound of claim
1,2,3,4,5 or 6.

9.   A method of lowering nitric oxide levels in a
30   subject in need of such by administering a
therapeutically effective amount of a compound of claim
1,2,3,4,5 or 6.

10.   A method of lowering nitric oxide levels in a
35   subject in need of such by administering a
therapeutically effective amount of a pharmaceutical
composition comprising a compound of claim 1,2,3,4,5, or

6 and together with at least one non-toxic pharmaceutical acceptable carrier.

11. A pharmaceutical composition comprising a
5 compound of claim 1,2,3,4,5 or 6 and together with at least one non-toxic pharmaceutical acceptable carrier.

.

12. A compound having the formula:
10
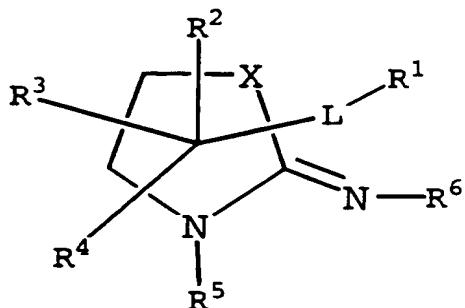
and salts, pharmaceutically acceptable esters and
15 prodrugs thereof, wherein:

R^1 is selected from the group consisting of cycloalkyl, heterocyclyl, and aryl, which may optionally be substituted by one or more of lower alkyl, lower alkenyl, lower alkynyl,
20 hydroxy, lower alkoxy, thiol, lower thioalkoxy, amino, aminoalkyl, aminoaryl, carboxyl, carboalkoxy, carboaryloxy, aminocarbonylalkoxy, aminocarbonylamino, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, amino, aminoalkyl, aminoacyl,
25 carboxyl, carboalkoxy, carboaryloxy, hydroxy, lower alkoxy, and

L is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, which may
30 optionally be substituted by one or more of the following: lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, amino,

aminoalkyl, aminoaryl, carboxyl, carboalkoxy,
carboaryloxy, aminocarbonylalkoxy, aminocarbonylamino,
wherein all said substitutions may be optionally
substituted with one or more of the following: lower
5   alkyl, amino, aminoalkyl, aminoacyl, carboxyl,
carboalkoxy, carboaryloxy, hydroxy, lower alkoxy, nitro,
amidino, guanidino, substituted guanidino;

X is selected from the group consisting of NH, O, S,
10 $(CH_2)_p$, CH=CH;

p = 0 to about 3;

R^2, R^3, and R^4 are independently selected from hydrogen,
15 lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower
alkoxy, thiol, lower thioalkoxy, amino, aminoalkyl,
aminoaryl, carboxyl, carboalkoxy, carboaryloxy,
aminocarbonylalkoxy, aminocarbonylamino, wherein all said
substitutions may be optionally substituted with one or
20 more of the following: lower alkyl, amino, aminoalkyl,
aminoacyl, carboxyl, carboalkoxy, carboaryloxy, hydroxy,
lower alkoxy, and

R^5, R^6 are independently selected from the group
25 consisting of hydrogen, hydroxy, and alkyloxy.

13.   A compound having the formula:

30
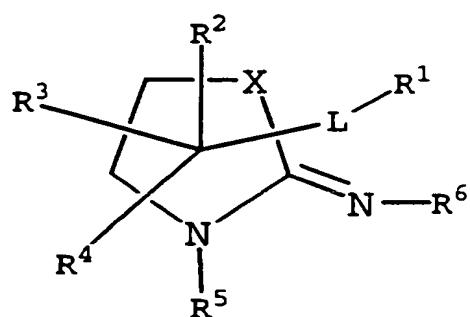
and salts, pharmaceutically acceptable esters and
prodrugs thereof, wherein:

R^1 is selected from the group consisting of cycloalkyl,
5   heterocyclyl, and aryl, which may optionally be substituted
by one or more of lower alkyl, lower alkenyl, lower alkynyl,
hydroxy, lower alkoxy, thiol, lower thioalkoxy, amino,
aminoalkyl, aminoaryl, carboxyl, carboalkoxy, carboaryloxy,
aminocarbonylalkoxy, aminocarbonylamino, wherein all said
10   substitutions may be optionally substituted with one or more
of the following: lower alkyl, amino, aminoalkyl, aminoacyl,
carboxyl, carboalkoxy, carboaryloxy, hydroxy, lower alkoxy,
and

15   L is selected from the group consisting of lower
alkylene, lower alkenylene, lower alkynylene, which may
optionally be substituted by one or more of the
following: lower alkyl, lower alkenyl, lower alkynyl,
hydroxy, lower alkoxy, thiol, lower thioalkoxy, amino,
20   aminoalkyl, aminoaryl, carboxyl, carboalkoxy,
carboaryloxy, aminocarbonylalkoxy, aminocarbonylamino,
wherein all said substitutions may be optionally
substituted with one or more of the following: lower
alkyl, amino, aminoalkyl, aminoacyl, carboxyl,
25   carboalkoxy, carboaryloxy, hydroxy, lower alkoxy, nitro,
amidino, guanidino, substituted guanidino;

X is selected from the group consisting of $(CH_2)_p$;

30   p = 1 to 3;

R^2, R^3, and R^4 are independently selected from hydrogen,
lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower
alkoxy, thiol, lower thioalkoxy, amino, aminoalkyl,
35   aminoaryl, carboxyl, carboalkoxy, carboaryloxy,
aminocarbonylalkoxy, aminocarbonylamino, wherein all said
substitutions may be optionally substituted with one or
more of the following: lower alkyl, amino, aminoalkyl,

aminoacyl, carboxyl, carboalkoxy, carboaryloxy, hydroxy, lower alkoxy, and

R^5, R^6 are independently selected from the group
5   consisting of hydrogen, hydroxy, and alkyloxy.

14.   The compound as defined in Claim 13 wherein
the compound is selected from a preferred group
consisting of N-[2-(hexahydro-7-imino-1H-azepin-2-
10 yl)ethyl]-3,4-dihydro-2H-pyrrol-5-amine,
bis(trifluoroacetate) salt; hexahydro-7-imino-β-phenyl-
1H-azepine-2-ethanamine, bis(trifluoroacetate) salt;
hexahydro-7-imino-β-(2-thienyl)-1H-azepine-2-ethanamine,
bis(trifluoroacetate) salt; hexahydro-7-imino-β-(3-
15 thienyl)-1H-azepine-2-ethanamine, bis(trifluoroacetate)
salt; hexahydro-7-imino-β-(2-furanyl)-1H-azepine-2-
ethanamine, bis(trifluoroacetate) salt; N-[2-(hexahydro-
7-imino-1H-azepin-2-yl)-2-phenylethyl]guanidine,
bis(trifluoroacetate) salt; 4,5-dihydro-5-[(hexahydro-7-
20 imino-1H-azepin-2-yl)methyl]isoxazole-3-carboxylic acid,
monohydrochloride; 7-[(4,5-dihydro-3-phenylisoxazolyl-5-
yl)methyl]hexahydro-2H-azepine-2-imine,
monotrifluoroacetic acid salt; hexahydro-7-[2-(4-
pyridinyl)ethyl]-2H-azepin-2-imine, monohydrochloride;
25 hexahydro-7-[2-(1-methylpiperidin-2-yl)ethyl]-2H-azepin-
2-imine, dihydrochloride; hexahydro-7-[2-(2-
piperidinyl)ethyl]-2H-azepin-2-imine, dihydrochloride; 1-
[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1H-tetrazole,
trifluoroacetate salt; N-[2-(hexahydro-7-imino-1H-azepin-
30 2-yl)ethyl]-3,4,5,6-tetrahydro-2H-azepin-7-amine,
bis(trifluoroacetate) salt; N-[2-(hexahydro-7-imino-1H-
azepin-2-yl)ethyl]-2,3,4,5-tetrahydropyridin-6-amine,
bis(trifluoroacetate) salt; hexahydro-N-(hexahydro-1H-
azepin-2-ylidene)-7-imino-β-phenyl-1H-azepine-2-
35 ethanamine, bis(trifluoroacetate) salt; hexahydro-N-
(hexahydro-1H-azepin-2-ylidene)-7-imino-β-(2-thienyl)-1H-
azepine-2-ethanamine, bis(trifluoroacetate) salt; N-[2-
(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-4,5-dihydro-1H-

imidazol-2-amine, bis(trifluoroacetate) salt; N-[2-
(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1,4,5,6-
tetrahydropyrimidin-2-amine, bis(trifluoroacetate) salt;
2-[(hexahydro-7-imino-1H-azepin-2-yl)methyl]benzenamine,

5   dihydrochloride; N-[2-(hexahydro-7-imino-1H-azepin-2-
yl)ethyl]-3,4-dihydro-2-methyl-2H-pyrrol-5-amine,
bis(trifluoroacetate) salt; N-[2-(hexahydro-7-imino-1H-
azepin-2-yl)ethyl]-3,4-dihydro-4-methyl-2H-pyrrol-5-
amine, bis(trifluoroacetate) salt; 2-[(hexahydro-7-

10   imino-1H-azepin-2-yl)methyl]cyclohexanamine,
dihydrochloride; 6-(cyclohexylmethyl)piperidin-2-imine,
monohydrochloride; (±)(trans) 4-methyl-5-
(phenylmethyl)pyrrolidin-2-imine, monohydrochloride;
trans-N-[3-(5-imino-3-methylpyrrolidin-2-

15   yl)propyl]benzenamine, dihydrochloride.

15.   The compound as in Claim 13 wherein the
compound is selected from a most preferred group
consisting of hexahydro-7-[2-(2-piperidinyl)ethyl]-2H-

20   azepin-2-imine, dihydrochloride; N-[2-(hexahydro-7-
imino-1H-azepin-2-yl)ethyl]-3,4-dihydro-2H-pyrrol-5-
amine, bis(trifluoroacetate) salt; hexahydro-7-imino-β-
phenyl-1H-azepine-2-ethanamine, bis(trifluoroacetate)
salt; 1-[2-(hexahydro-7-imino-1H-azepin-2-yl)ethyl]-1H-

25   tetrazole, trifluoroacetate salt; hexahydro-7-imino-β-
(2-thienyl)-1H-azepine-2-ethanamine,
bis(trifluoroacetate) salt; trans-N-[3-(5-imino-3-
methylpyrrolidin-2-yl)ethyl]phenylmethylamine,
dihydrochloride; hexahydro-7-imino-N-(2-

30   pyrrolidinylidene)-β-(2-thienyl)-1H-azepine-2-
ethanamine, bis(trifluoroacetate) salt; hexahydro-N-
(hexahydro-1H-azepin-2-ylidene)-7-imino-β-phenyl-1H-
azepine-2-ethanamine, bis(trifluoroacetate) salt; and 2-
[(hexahydro-7-imino-1H-azepin-2-

35   yl)methyl]cyclohexanamine, dihydrochloride

16.   The compound as in Claim 15 wherein the
compound is hexahydro-7-[2-(2-piperidinyl)ethyl]-2H-
azepin-2-imine, dihydrochloride.

5   17.   The compound as in Claim 15 wherein the
compound is N-[2-(hexahydro-7-imino-1H-azepin-2-
yl)ethyl]-3,4-dihydro-2H-pyrrol-5-amine,
bis(trifluoroacetate) salt.

10   18.   The compound as in Claim 15 wherein the
compound is hexahydro-7-imino-β-phenyl-1H-azepine-2-
ethanamine, bis(trifluoroacetate) salt.

           19.   The compound as in Claim 15 wherein the
15   compound is 1-[2-(hexahydro-7-imino-1H-azepin-2-
yl)ethyl]-1H-tetrazole, trifluoroacetate salt.

           20.   The compound as in Claim 15 wherein the
compound is trans-N-[3-(5-imino-3-methylpyrrolidin-2-
20   yl)ethyl]phenylmethylamine, dihydrochloride.

           21.   The compound as in Claim 15 wherein the
compound is hexahydro-7-imino-β-(2-thienyl)-1H-azepine-2-
ethanamine, bis(trifluoroacetate) salt.

25

           22.   The compound as in Claim 15 wherein the
compound is hexahydro-N-(hexahydro-1H-azepin-2-ylidene)-
7-imino-β-phenyl-1H-azepine-2-ethanamine,
bis(trifluoroacetate) salt.

30

           23.   The compound as in Claim 15 wherein the
compound is hexahydro-7-imino-N-(2-pyrrolidinylidene)-β-
(2-thienyl)-1H-azepine-2-ethanamine,
bis(trifluoroacetate) salt.

35

24.   The compound as in Claim 15 wherein the
compound is 2-[(hexahydro-7-imino-1H-azepin-2-
yl)methyl]cyclohexanamine, dihydrochloride

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6	C07D223/12	A61K31/55	C07D405/06	C07D409/06	C07D207/14
	C07D225/02	C07D211/72	C07D413/06	C07D403/06	C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6   C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,95 11231 (SEARLE) 27 April 1995 * see claim 1 and Examples 263, 272, 301, 302 * ---	1
Y	WO,A,94 12165 (THE WELLCOME FOUNDATION) 9 June 1994 cited in the application	1
X	* see formulae (IA) and (IC) * ---	1
Y	WO,A,94 14780 (THE WELLCOME FOUNDATION) 7 July 1994 cited in the application see claims 1,2 --- -/--	1

[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 1996	14. 08. 96

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Lauro, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. HETEROCYCLIC CHEM., vol. 19, no. 1, 1982, pages 193-200, XP002009271 M. LANGLOIS ET AL.: "Synthèse de nouvelles amidines bicycliques. 1. Dérivés de l'imidazole, du triazole-1,3,4 et du tétrazole" * see compound 10 * ---	1
A	WO,A,93 13055 (THE WELLCOME FOUNDATION) 8 July 1993 cited in the application see claim 1 -----	1

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9511231	27-04-95	AU-B-	8081194	08-05-95
		NO-A-	961403	09-04-96
WO-A-9412165	09-06-94	AU-B-	5533094	22-06-94
		CN-A-	1095710	30-11-94
		EP-A-	0670720	13-09-95
		JP-T-	8503940	30-04-96
		SI-A-	9300616	30-06-94
		ZA-A-	9308867	26-05-95
WO-A-9414780	07-07-94	AU-B-	5704594	19-07-94
		EP-A-	0674627	04-10-95
		JP-T-	8504798	21-05-96
		US-A-	5459158	17-10-95
		ZA-A-	9309480	19-06-95
WO-A-9313055	08-07-93	AU-B-	669345	06-06-96
		AU-B-	3169293	28-07-93
		EP-A-	0618898	12-10-94
		HU-A-	70502	30-10-95
		JP-T-	7502512	16-03-95
		NZ-A-	246202	28-05-96
		ZA-A-	9210018	23-06-94

1996:758969   Document No. 126:31278   Preparation of iminoazepines and related cyclic amidines useful as nitric oxide synthase inhibitors..   Hansen, Donald W., Jr.; Hallinan, E. Ann; Hagen, Timothy J.; Kramer, Steven W.; Metz, Suzanne; Peterson, Karen B.; Spangler, Dale P.; Toth, Mihaly V.; Fok, Kam F.; et al. (G.D. Searle and Co., USA; Hansen, Donald W., Jr.; Hallinan, E. Ann; Hagen, Timothy J.; Kramer, Steven W.; Metz, Suzanne; Peterson, Karen B.; Spangler, Dale P.; Toth, Mihaly V.; et al.).   PCT Int. Appl. WO9633175 A1 961024, 299 pp.
DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English).   CODEN: PIXXD2.   APPLICATION: 96WO-US05315 960419.   PRIORITY: 95US-0425831 950420.

IT   ***184365-39-7P***

       (prepn. of iminoazepines and related cyclic amidines useful as nitric oxide synthase inhibitors)

RN   184365-39-7   ZCAPLUS
CN   Piperidine, 2-[2-(7-amino-3,4,5,6-tetrahydro-2H-azepin-2-yl)ethyl]-1-(methylsulfonyl)-, mono(trifluoroacetate) (9CI)   (CA INDEX NAME)

    CM   1

    CRN   184365-38-6
   CMF $C_{14}H_{27}N_3O_2S$
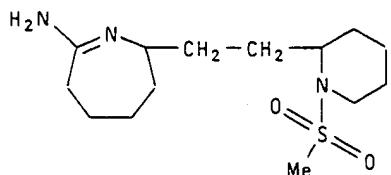


    CM   2

    CRN   76-05-1
    CMF $C_2HF_3O_2$
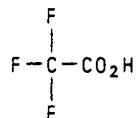
RN   184365-39-7   ZCAPLUS

IT   ***184367-11-1P***
   (prepn. of iminoazepines and related cyclic amidines useful as nitric oxide synthase
        inhibitors)
RN   184367-11-1   ZCAPLUS
CN   Piperidine, 2-[2-(hexahydro-7-oxo-1H-azepin-2-yl)ethyl]-1-(methylsulfonyl)- (9CI)   (CA INDEX
        NAME)
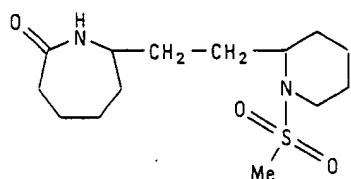
GI
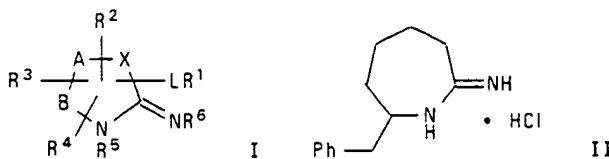
AB   Title compds. [I; R^1 = (substituted) cycloalkyl, heterocyclyl, aryl; R^2-R^4 = H, (substituted)
        alkyl, alkenyl, alkynyl, OH, alkoxy, SH, alkylthio, amino, NO$_2$, cyano, arylamino, alkylamino,
        acylamino, arylamino, haloalkyl, SO$_2$NR^{7}R^9, etc.; R^5, R^6 = H, OH, alkoxy; R^7 = H, alkyl, aryl;
        R^8 = H, alkyl, COR^9, CO$_2$R^9; R^9 = alkyl, aryl; L = (substituted) alkylene, alkenylene,
        alkynylene, (CH$_2$)$_m$D(CH$_2$)$_n$; D = O, S, SO, SO$_2$, SO$_2$NR^7, NR^{7}SO$_2$, NR^8, POOR^7, PON(R^7)$_2$,
        POOR^{7}NR^7, NR^{7}POOR^7, CO, CO$_2$; B = (CH$_2$)$_v$, CH:CH; A = O, NR^7, (CH$_2$)$_q$, CH:CH; X = NH, O,
        S, (CH$_2$)$_p$, CH:CH; m = 0-7; n = 0-5; p = 0-4; q = 1, 2], were prepd.   Thus,
        2-benzylcyclohexanone was converted to the oxime, which was heated in 80% aq. H$_2$SO$_4$ to
        give a mixt. of 3- and 7-benzylcaprolactam.   The 7-benzyl isomer was treated with
        Me$_3$OBF$_4$ and mol. sieves to give the methoxyimine, which was refluxed with NH$_4$Cl in MeOH
        to give title compd. (II).   II inhibited human inducible nitric oxide synthase with IC$_{50}$ = 6.2
        μM.

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